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STUDIES ON THE METABOLISM AND DISPOSAL OF AMINO ACID MIXTURES GIVEN INTRAVENOUSLY

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IN VIEW of the increasing use of various types of amino acid solutions as sources of protein, there is need for a clearer understanding of the metabolism of these substances and the manner by which their metabolic end-products are excreted. Such a study has been undertaken with the objective of securing information that would add to the efficiency and safety with which amino acid preparations could be used in clinical practice. The present report deals with the results of a series of animal experiments that simulate in many respects the circumstances encountered in patients.

That positive nitrogen balance as well as plasma protein regeneration can be produced during the administration of amino acid solutions as the sole source of nitrogen is no longer questioned. This result has been accomplished by various routes of administration —oral, intravenous, subcutaneous and intraperitoneal. Crystalline amino acid solutions as well as hydrolysates of complete proteins such as casein have given satisfactory results. Conclusive experiments have been carried out both on human beings and experimental animals. The value of amino acid preparations as an aid to hemoglobin regeneration and as an adjunct in the treatment of shock has also been reported. The literature covering the many studies on amino acid metabolism and clinical uses of amino acids has been reviewed elsewhere.[1-5] There can be no doubt that amino acid preparations offer an efficient substitute for protein in a variety of conditions.

A majority of studies on the metabolism and utilization of amino acid preparations have dealt with the ability to approach or maintain nitrogen equilibrium or to promote regeneration of blood proteins. This type of experiment requires long term observations and data on intake and output from which nitrogen balances can be calculated. While balance studies may demonstrate the gross usefulness of a preparation, they contribute

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little toward an understanding of the dynamic factors which influence efficiency of utilization following short periods of administration. These latter can be approached through a study of the dynamic changes which accompany infusions.

In clinical medicine amino acid preparations have found their greatest value as a substitute for protein in cases where ingestion by the oral route is impossible. Nitrogen is often supplied through 1, 2 or 3 intravenous infusions a day, each of which continues for ½ to 2 hours. In some instances attempts are made to spread the infusion over a larger portion of the day. Relatively little attention has been given to the fate of such infusions although it is clear that the rates of destruction and elimination of the infused material will determine the final value of the procedure.

The experiments presented below are designed to investigate the changes which take place during infusions which continue at a constant rate over a period of several hours and in some instances during an after-period as well. Although the data permit the calculation of only approximate nitrogen balances, they elucidate other aspects of the metabolism and disposal of the preparations which, it is hoped, will add to efficiency and safety in their clinical use. For convenience the experimental data will be presented under the following headings: (a) fate of the infused amino acids (b) renal function and (c) respiratory metabolism. Water balance will be discussed in a subsequent report.

Experimental Procedures

The basic experiment consisted in the constant intravenous infusion of 1.0 gm. of a casein hydrolysate*/kg./hr. over a period of 8 hr. With a few exceptions, male New Zealand white rabbits were used throughout. The infusions were made into a marginal ear vein by means of a mechanical pump at the rate of 10 cc./kg./hr., the amino acid preparation being a 10% solution. The animals had been operated on previously and a glass cannula inserted into the bladder to permit continuous collection of urine. Not less than 2, nor more than 5 days, were allowed for recovery, following which the animal was fasted overnight and the infusion started early the following morning. Aside from the preliminary surgery, no anesthetics were employed, and throughout the experiments the animals behaved in a normal manner. Several types of infusions were used which varied in composition or concentration in order to obtain comparative data.

During the infusion, and in some instances during an after-period, observations were made on both urine and blood. Urine volume was measured at half-hour intervals and combined into pools representing successive 2 hr. periods. On these pools the total nitrogen was partitioned into the amino, urea and ammonia components. At intervals representing 0, 2, 6 and 8 hr. after the beginning of the infusion 3 to 5 cc. of blood were collected from an ear vein for the estimation of amino acid nitrogen, urea nitrogen, total NPN, plasma protein, and carbon dioxide combining power. These times were selected because they represented the beginning and end of the first and last periods of the infusion.

The chemical methods employed were standard ones. Urine analyses for total nitrogen were determined by the micro-Kjeldahl method, urea and ammonia by the aeration method of Van Slyke†[6] and amino acid nitrogen by the method of Albanese and Irby.[7,8] The Folin micromethod[9] was used for blood NPN. The Conway method was employed for blood urea[10] and the Lowry and Hunter gradient tube for plasma protein concentration as well as for urine specific gravity.[11]

Results

Figure 1 illustrates the type of experiment performed and presents the average results obtained from 16 animals which received a 10% solution of casein hydrolysate. It will be noted that the blood amino nitrogen level rose sharply during the first two hours

* Amigen was made available through the courtesy of Mead Johnson and Company.

† Method was modified by using 15 cc. of 1% boric acid solution instead of 25 cc. of .02 N HCl and was titrated with .01 N HCl rather than .02 N NaOH.

of the infusion and remained at a fairly constant level throughout the remaining six hours. Blood urea, on the other hand, rose more slowly and had not reached a plateau at the end of the eight hours of infusion. In spite of the rather large dose of casein hydrolysate the carbon dioxide combining power showed essentially no change in an average of 16 experiments. At the pH of 6.5 to which the hydrolysate has been adjusted commercially,

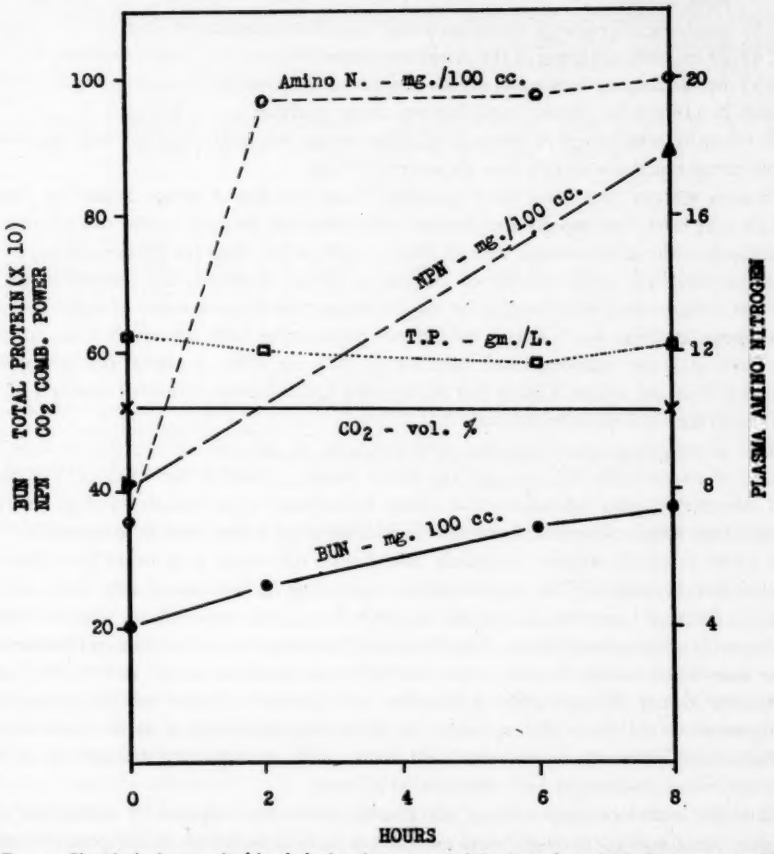


FIG. 1. Chemical changes in blood during intravenous injection of casein hydrolysate to rabbits. Figures are averages obtained from 16 animals which received 1 gm. of hydrolysate in 10% solution/kg./hr.

the buffering mechanisms of the body appeared to be adequate. There was a slight fall in plasma protein concentration but probably not more than could be accounted for by the withdrawal of blood and the dilution caused by the infusion. It will be noted that the NPN of the blood rose more in proportion than did the urea fraction. Part of this is, of course, due to the increased level of amino nitrogen, but probably even more important is the fact that approximately 30% of the hydrolysate was in the form of peptide nitrogen. This would be evident as part of the nonprotein fraction and would account for the proportionally higher values.

Fate of the Infused Amino Acids

When amino acids are introduced into the circulation, there are several possible ways in which they may be dispersed and utilized. Amino acids may:

(1) remain in the circulatory system after mixing and consequent dilution;
(2) become distributed by simple diffusion throughout the extra- and intra-cellular body fluids;
(3) reach the liver and be deaminated with resultant formation of urea;
(4) be excreted unaltered in the urine, i.e., wasted;
(5) be taken up by tissues and organs and stored temporarily;
(6) be utilized for protein formation and tissue synthesis.

The extent to which each of these possibilities occurs warrants attention and the present experiments bring new facts to bear on several of them.

Within a short time after the beginning of an infusion of amino acids, the plasma amino acid level rises rapidly and reaches a height which depends on the rate of infusion and the quantity administered. Part of this increase occurs from the simple mixing of the infusion with the larger volume of circulating blood. However, the proportion of the infused amino nitrogen remaining in the circulating plasma at the end of eight hours of continuous injection was found in the present experiments to be very small. Calculated on the basis of a rise in blood level from 7.0 to 19.3 mg./100 cc. blood, this amounts to only 1.4% of the intake. Clearly retention in the blood stream accounts for only a minor portion of the total quantity infused.

The investigations here reported shed no light on the rate of distribution into the tissues of amino acids injected into the blood stream. However, the work of Van Slyke and Meyer,[12,13] who administered a casein hydrolysate intravenously to dogs, demonstrated that within 30 minutes the tissues had taken up a considerable proportion. This was either in simple solution or loosely bound since the amino acids could be readily extracted and determined. The tissues shown to be active in this respect were liver, muscle, kidney, intestine, pancreas and spleen. In somewhat similar experiments with individual amino acids administered to rats, Friedberg and Greenberg[14] and Handler and Kamin[15,16] have shown that within 15 minutes 80 to 90% leaves the blood stream and can be identified in the tissues although individual amino acids distribute themselves characteristically. Christensen et al.[17] have clarified some of the factors concerned with the characteristic distributions. There can be no doubt that amino acids are rapidly distributed to the tissues and remain unchanged for a short period of time.

Since the amino nitrogen level of the plasma is increased appreciably during such infusions, some wastage through renal excretion is to be anticipated. In the present studies where the infusions were given at a constant rate over a period of eight hours this was not great. As will be seen in table 1, the loss in the urine amounted to 30 mg./kg. or 4.8% during the infusion and to a total of 6.0% including the six hour after-period. These figures are in good agreement with those of Van Slyke and Meyer[12,13] for dogs. Other studies[18,19] have demonstrated that with more rapid infusions loss through the urine may reach as high as 20%. It seems clear, therefore, that in the present type of experiment wastage through renal excretion and retention in the blood stream account for less than 8% of the mixture infused into the circulation. A far larger amount passes quickly into the tissues where it remains temporarily in a relatively free and unchanged state, eventually becoming incorporated in tissue protein or returned to the liver, deaminated, and excreted as urea in the urine. The rate and completeness of this latter proc-

TABLE 1

ELIMINATION OF NITROGEN AFTER INTRAVENOUS ADMINISTRATION OF CASEIN HYDROLYSATE

Data Obtained from Rabbits During Intravenous Administration of Casein Hydrolysate over 8 Hour Period and 6 Hour After-Period. Figures are averages for 16 rabbits which received infusion for 8 hr. period and 3 others in which infusion was continued during 6 hr. after-period

2 hr. periods	Cumulative intake		Cumulative output in urine			Cumulative retention in body fluids*		Percentage nitrogen waste†	
	NH_3-N mg./kg.	Total N mg./kg.	NH_3-N mg./kg.	Urea-N mg./kg.	Total N mg./kg.	Urea-N mg./kg.	Total N mg./kg.	Urea-N %	Total NPN %
0	0	0	0.5	47	55	—	—	—	—
I	163	250	5	59	90	47	106	43	78
II	318	488	12	146	218	—	—	—	—
III	468	720	21	256	369	104	—	53	—
IV	637	964	30	381	545	118	332	55	91
V	0	0	35.5	464	647	189	—	72	—
VI	0	0	36.5	537	731	165	195	77	96
VII	0	0	37.5	576	795	125	125	77	95

* Calculated from concentration found in blood, assuming distribution in 70% of body weight. Loss of nitrogen in stool has been neglected.

† Percentage nitrogen waste $= \frac{\text{N excreted in urine} + \text{N accumulated in body fluids} \times 100}{\text{N intake}}$

ess will determine in fair measure the usefulness of the infusion to the total economy of the body.

The rate at which the infused hydrolysate is deaminated is difficult to determine accurately because of the impossibility of distinguishing between urea formed from the administered material and that resulting from so-called endogenous sources. However, some indication of this is obtained from the fact that a distinct rise in blood urea was observed during the first two hours of the infusion. Furthermore, the rate of excretion of urea in the urine increased sharply during the same period but in no way kept pace with the rate of nitrogen injection. This lag in the deamination process has been pointed out many times by others.

An estimation of the extent to which deamination proceeds can be obtained from data on the output of urea in the urine and on the accumulation in body fluids. In table 1 it will be seen that by the end of the eighth hour of the infusion (Period IV), 55% of the total nitrogen intake could be accounted for as urea excreted in the urine or retained in the body fluids, and during the six hour after-period the proportion rose to 77%. The corresponding figures for total nitrogen excretion were 91 and 95%, respectively. It is of course impossible to state what part of these totals represents a basic endogenous loss that might go on in spite of the infusion. However, in the presence of a surfeit of infused amino acids it seems probable that this loss would be minimal; it might well increase during the after-period. It would seem reasonable to conclude that the total amount of infused material which is deaminated or excreted, and thus is not utilized for tissue construction under the circumstances of these experiments, falls somewhere between 70 and 85% in the present type of experiment.

That under certain circumstances deamination may proceed to such an extent that the free amino acids remaining in the body are inadequate to support all needs has been demonstrated indirectly by numerous workers[20-24] in animal experiments. They have shown that an interval of 1 to 6 hours between the administration of all but a single essential amino acid and that single acid interferes significantly with total retention and utilization. These observations become understandable in the light of the experiments reported here which show that during such an interval a large part of infused amino acids are deaminated and thus no longer available for tissue synthesis.

One can only conclude that following the infusion or ingestion of amino acid mixtures the rate of deamination is rapid and that after the administration is stopped, the beneficial effects may be quickly expended. The experiments reported here were carried out

TABLE 2

COMPARISON OF EFFECTS OF CASEIN HYDROLYSATE ADMINISTERED BY PERIPHERAL AND BY MESENTERIC VEINS

Site of Infusion	No. of Animals	Intake mg./kg.	Output mg./kg.		Increase mg./100 cc.	
		Total N	Total N	Amino N	Plasma Amino N	Blood Urea N
Peripheral Vein	12	490	217	12.2	12.3	10.7
Mesenteric Vein	5	505	207	16.4	15.4	16.8

Rabbits received 10% solution at rate of 10 cc./kg./hr. for 4 hr.

on animals without protein deficiency; hypoproteinemic animals and undernourished human beings might well show greater retention and less wastage.

Since amino acid mixtures are commonly introduced into a peripheral vein instead of the portal system as in normal protein metabolism, a question has been raised concerning the effects of the route of administration on the results obtained. A series of experiments was therefore carried out in which the 10% casein hydrolysate was delivered into a mesenteric vein and hence directly to the liver. The animals were kept under a light amytal anaesthesia but in other respects the procedures were the same as described above. Table 2 shows that although the amino acid mixture was delivered directly to the liver and was thus exposed immediately to the deaminating action of this organ, the rise in amino nitrogen in the peripheral blood was essentially the same as when the injection was made into a peripheral vein. It is of interest to note that blood urea rose more rapidly when the hydrolysate was delivered directly into the portal system. Total nitrogen intake and output figures were essentially the same in the two groups of experiments. One must conclude that the quantitative as well as qualitative aspects of amino acid metabolism are essentially the same whether the solution is administered into the peripheral or portal circulation. A similar conclusion was reached in experiments with goats carried out by Henriques and Anderson.[25]

It was observed by Van Slyke and Meyer[12,13] that following an intravenous infusion of a casein hydrolysate the various organs and tissues of the dog showed an increased level of relatively free amino nitrogen. In the liver this additional nitrogen quickly returned toward normal, supposedly as a result of deamination, but in other organs such as muscle

and kidney, the high level persisted as long as 3½ hours after the end of the infusion. Obviously, this indicates temporary storage of amino acids, but whether it represents merely diffusion out of the blood stream or a loose combination in the first stages of protein synthesis cannot be stated. That storage of all the essential amino acids does not continue beyond six hours in the dog and one hour in the rat is evident from the work of others mentioned above.[20–24] The experiments reported here do not bear directly on the question of how long all of the infused essential amino acids remain available in the stores. However, it is evident from the decreasing output of urea in the urine following the cessation of the infusion that the amount of amino acids available for deamination in the liver has markedly decreased within four hours—table 1. Furthermore, the surplus amino acid nitrogen circulating in the blood disappeared 2 to 4 hours after the cessation of the infusion. From the evidence at hand, therefore, it must be concluded that only for a few hours following an infusion of hydrolysate is there a sufficient quantity and variety of amino acids stored to permit tissue synthesis to proceed.

The experiments used in the present study were too short to permit conclusions regarding amino acid retention for tissue synthesis. They have demonstrated only that in normal animals during the course of an eight hour infusion and an after-period most of the infused nitrogen has appeared in the urine, and the amount remaining in the body for possible tissue formation is relatively small. Under conditions of protein depletion such as occur in disease and following prolonged protein deprivation, the situation may be different. Long term studies by various workers have demonstrated nitrogen retention under these circumstances following either protein or amino acid administration. The rate of nitrogen retention, however, even under the most extreme conditions amount to only a fraction of a gram of nitrogen/kg./day. In contrast to this, the quantity of amino nitrogen administered by parenteral routes has sometimes reached a rate as high as 2.8 gm./kg./hr. for short periods and a total of 3.5 gm./kg./day.[26] What the optimal conditions are for nitrogen retention and how much must be infused daily to give the most efficient utilization cannot be stated. The investigations discussed in this report and elsewhere[20–24] would lead one to suspect that relatively small amounts of a complete mixture of amino acids given continuously over a relatively long period might accomplish more in the way of protein synthesis than larger but intermittent doses.

Renal Function

The safety of large infusions of amino acid mixtures will depend in fair measure on the capacity of the kidney to eliminate the end-products rapidly and efficiently. During the experiments described in the preceding section several observations were made which raised questions concerning the ability of the kidney to deal with high nitrogen loads. In the first place, nitrogen retention in the blood became quite marked in spite of a good and continuous flow of relatively dilute urine. Secondly, the blood urea level remained high many hours after the cessation of the infusion even though water intake was unrestricted and output of urine was normal. And, finally, since the amino acid infusions tended to decrease urine flow for several hours, the possibility presented itself that high concentrations of amino acids in the blood might have some specific injurious effect on the kidney. It became important, therefore, to investigate renal function during the continuous infusions of casein hydrolysate to provide a basis for judging the safety of such forms of therapy in clinical medicine.

The technical procedures described above offered opportunities to observe three aspects

of renal function, viz., (a) amino acid clearance, (b) urea clearance and (c) water excretion and urine concentration. The stability of the experimental conditions during the continuous eight hour infusions was particularly favorable for such observations. In all instances the rate of injection/kg. animal weight was maintained constant. In one series of experiments the infusion was the same as in the previous section, viz., 10 cc. 10%

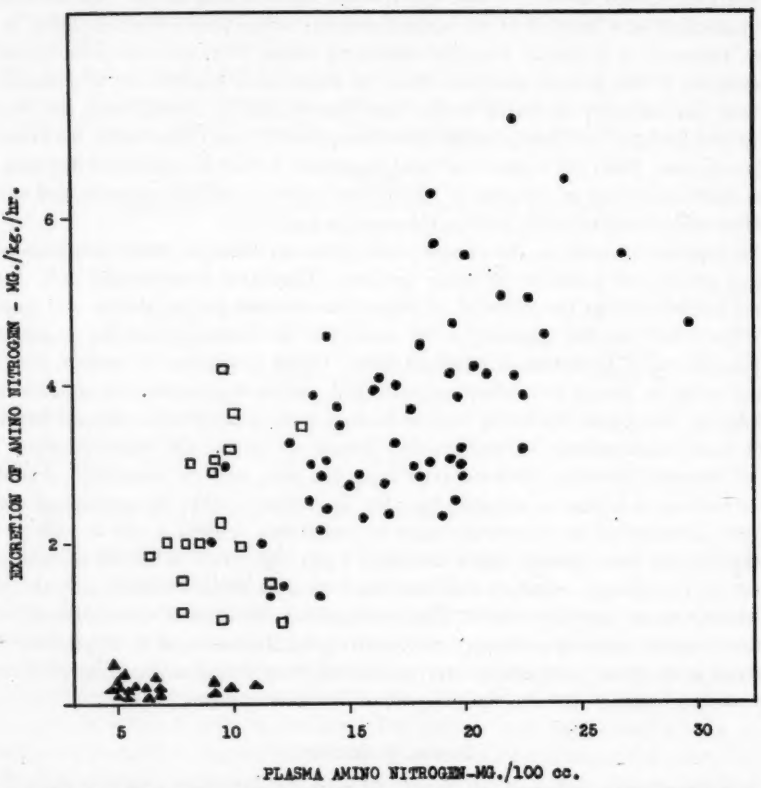


FIG. 2. Relationship between plasma amino nitrogen level and rate of excretion in urine.
● = rabbits receiving 10% amigen
□ = 5% amigen in 5% glucose
▲ = physiologic saline

casein hydrolysate/kg./hr. In a second series the same amount of nitrogen was administered in the form of urea (2.57%) in physiologic saline solution and in a third group physiologic saline alone was given. The salt content of the hydrolysate was approximately one-half that of physiologic saline but this difference does not appear to have significance in determining the results.

The data on blood amino nitrogen level and rate of excretion of amino nitrogen in the urine as observed in all types of experiments have been presented in figure 2. It will be noted that as the level of plasma amino nitrogen increases the rate of excretion in the urine also increases. Although there is considerable scatter among the points a straight line relationship similar to normal urea clearance is suggested.

Calculation of amino nitrogen clearance during each of the experimental periods covering eight hours of infusion and a six hour after-period showed a good degree of constancy with no progressive change as the infusion continued. Pitts[27] and Goettsch et al.,[28,29] using a different technic, have reported a rise in amino nitrogen clearance at high plasma levels. While the present experiments do not lend themselves to confirmation of this observation, they in no way suggest impaired capacity of the rabbit kidney to excrete amino acids or injury to the kidney as a result of the large and prolonged infusions.

The relationship between urea level in the blood and rate of excretion in the urine was also observed during infusions of casein hydrolysate, urea in physiologic saline and

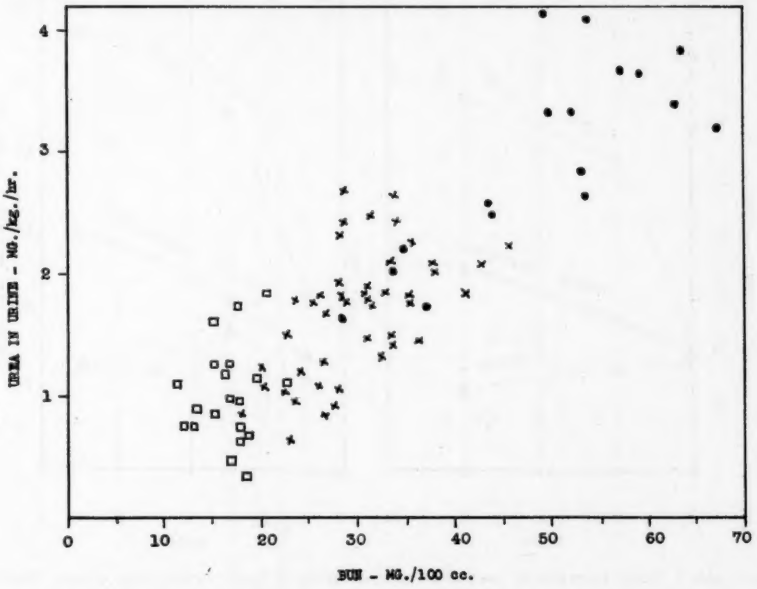
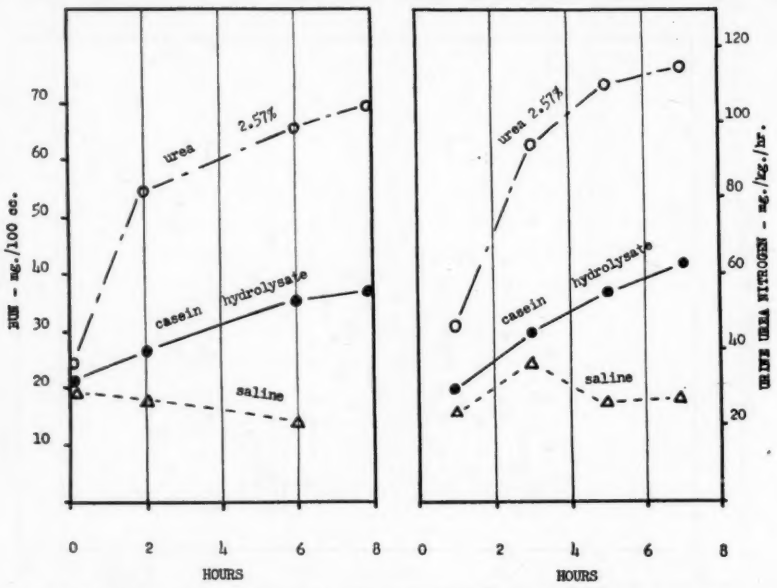


FIG. 3. Relationship between blood urea nitrogen level and rate of excretion in urine.
× = rabbits receiving 10% amigen
● = 2.57% urea in physiologic saline
□ = physiologic saline

physiologic saline alone. The results are presented in figure 3. Here again a straight line relationship is suggested. No differences are apparent between the hydrolysate and the urea experiments. One can conclude, therefore, that infusions of amino acid mixtures do not interfere with the ability of the kidney to excrete urea, and that the high levels of blood urea observed both during and after such infusions indicate only the normal lag in renal adjustment. This conclusion, however, should not excuse neglect in studying renal function of patients who are to receive infusions of amino acids. Existing renal disease would undoubtedly limit the amount of an amino acid mixture which could be safely administered.

It will be noted in figures 4 and 5 that higher levels of blood urea and a more rapid excretion of urea in the urine were obtained in animals receiving 2.57% urea in physio-

logic saline solution than when the same amount of nitrogen was infused in the form of casein hydrolysate. The reason for this difference becomes evident if three factors are taken into consideration: 1. Although the rate of deamination increases following the introduction of hydrolysate into the circulation, an appreciable amount of time is none the less required before the rate of urea formation reaches its maximum. Only after several hours is urea formed from the hydrolysate at a rate approaching the intake of urea in the urea experiments. In some measure this delay is undoubtedly due to the fact that part of the amino acids injected are absorbed by the tissues and retained there for several hours before finally reaching the liver where deamination takes place. 2. About 35% of the



FIGS. 4 and 5. Renal excretion of urea after administration of casein hydrolysate, urea in saline and saline alone.

● = 10% casein hydrolysate
○ = 2.57% urea in saline
Δ = physiologic saline
Rate of infusion was 10 cc./kg./hr.

total nitrogen of the hydrolysate used in the present studies is bound in the form of peptides. Christensen et al.[30] have shown that much of this peptide nitrogen is excreted unchanged but much more slowly than the nitrogen of the amino acids themselves. 3. Finally, some of the amino acids are utilized for protein formation and tissue synthesis. This part of the nitrogen intake thus becomes fixed and is not presented for excretion at all. In total quantity, this latter represents only a small part of the amount infused in the present experiment. It seems reasonable to conclude, therefore, that the lower levels of urea in both blood and urine found in the animals receiving hydrolysate as compared with an equivilent nitrogen load in the form of urea are due largely to differences in rate and quantity of the urea being presented for excretion and not to renal impairment.

Observations on the ability of the kidney to excrete water and concentrate urine indi-

TABLE 3

WATER BALANCE AFTER INFUSIONS OF CASEIN HYDROLYSATE AND UREA IN PHYSIOLOGIC SALINE

Infusions contained equal amounts of nitrogen during four 2 hr. periods. Figures for water balance represent differences between intake and urine volume and are somewhat higher than those obtained from changes in body weight during experiment

Period	Urine Volume cc./kg./hr.				Urine Specific Gravity				Total Os. Conc. m. os./l.				Total Water Balance cc./kg.
	I	II	III	IV	I	II	III	IV	I	II	III	IV	
Casein Hydrolysate	4.2	3.7	5.3	5.7	1.034	1.038	1.032	1.029	800	1018	800	802	+47
Urea in Physiologic Saline	6.7	9.3	10.5	9.4	1.011	1.016	1.016	1.017	586	860	758	777	+13
Physiologic Saline	1.6	6.7	6.2	6.3	1.032	1.021	1.018	1.014	1160	722	446	300	+39

cated no impairment in function during the eight hours of infusion of the hydrolysate. Water balance was somewhat more positive than when an equal amount of nitrogen was given in the form of urea in physiologic saline. However, as will be seen in table 3, specific gravity of the urine was consistently high during the infusion of hydrolysate and low during urea. Total solute concentration as measured by depression of freezing point was not significantly different.

Respiratory Metabolism

When large amounts of protein are fed by mouth, the respiratory quotient is consistently in the range of 0.80 to 0.82. Hydrolysates of proteins would be expected to result in similar quotients modified in some slight measure by oxygen and carbon dioxide changes which accompany the splitting up of the protein molecule. Direct observations, however, are limited. Lombroso and Ardy[31] studied a series of dogs and were unable to demonstrate significant differences in respiratory exchange between a casein hydrolysate adminis-

TABLE 4

Influence of Infusion of Casein Hydrolysate on Respiratory Quotient

Hours of infusion	0	2	4	6	8
Exp. 81	0.72	0.71	0.72	0.72	0.74
Exp. 82	0.81	0.78	0.74	0.72	0.74
Exp. 84	0.72	0.73	0.72	0.73	0.71
Average	0.75	0.74	0.73	0.72	0.73

Data were obtained during 8 hr. infusion of 10% casein hydrolysate.

tered orally or intravenously. Wilhelmj and Bollman[32] reported a definite rise in quotient following the injection of alanine, glycine and phenylalanine but the data cannot be interpreted with accuracy since changes in acid-base balance were not excluded. Observations on the specific dynamic action of several individual amino acids have been reported[33] but the data do not allow calculations of respiratory exchange. In view of the limited studies available in the literature, several carefully controlled experiments were carried out in the course of the work presented here. It was hoped that the data might shed further light on the metabolic fate of infusions of protein hydrolysates.

The animals were prepared as described above. On the morning of the experiment a tracheal cannula was inserted under local anesthesia according to a technic described previously.[34] The apparatus is equipped with valves which permit continuous or sample collections of expired air. Throughout the eight hours of observations the animal sits quietly in a box and acts normal in every way. Samples of expired air were collected for 10 to 20 minute periods every two hours during the infusions, and the analyses were carried out on a Haldane apparatus. The results are presented in table 4.

It will be seen that throughout the infusion the respiratory quotient remained at a level only slightly above that which is obtained during complete starvation or when the metabolic mixture is composed almost entirely of fat. In experiment No. 82, the control value of 0.81 gradually fell to the same level as in the other two experiments. The consistency of the results and the stability of the experimental conditions during the eight hours of continuous infusion indicate the reliability of the observations. Errors due to changes in

acid-base balance were ruled out by repeated determinations of carbon dioxide combining power which showed no change during the course of the experiments.

The values for respiratory quotient are distinctly lower than those to be expected following the ingestion of an equivalent amount of protein, viz., 0.81. An attempt was made to calculate the expected R.Q. from analyses of the individual amino acids known to be in the hydrolysate* and from present-day knowledge of the oxidative processes of each ingredient. Admittedly such calculations involve assumptions which cannot be substantiated in the present type of experiment. For example, because of the pressure of the large load of amino acids being infused and the rapidity of deamination, one can assume that this latter process is proceeding at a near maximum speed. However, no data are available as to what fraction of the whole is converted into glycogen and stored. The theoretic respiratory quotients for the individual amino acids range from 1.18 for aspartic acid to 0.50 for methionine. The calculated figure for the hydrolysate as a whole was 0.77 as contrasted to the observed value of 0.72 to 0.73. The difference between calculated and observed respiratory quotients may not be significant in view of the uncertainties and assumptions involved in the calculations. It is of interest, however, to find quotients in such a low range under conditions where deamination is proceeding at a maximal rate. It seems likely that the method might have additional value in determining the differences in fate of the individual amino acids when these become available in quantity.

Discussion

During the years that have elapsed since amino acid preparations became available commercially they have found wide use in clinical medicine as a substitute for food protein and have made complete parenteral feeding a practical procedure. Guides to quantity and schedule of administration, however, have been difficult to establish since the determination of gross nitrogen balance—the common basis for judgment—is a cumbersome and time-consuming procedure. As a result, empiric criteria have been set up based largely on clinical experience. While the results have been relatively satisfactory, the principle of "if a little is good, a lot is better" has often determined the plan of therapy without a full appreciation of the factors involved.

It is clear from studies reported in the literature and in the work presented above that quantity or dosage is not the only factor that determines the value and efficiency of amino acid preparations. If the rate of infusion is such that 70 to 85% of the material is de-

* The analysis of the casein hydrolysate was furnished by Dr. Warren M. Cox of Mead Johnson and Company and is as follows:

	per cent		per cent
Alanine	4.2	Lysine	5.3
Arginine	3.4	Methionine	2.7
Aspartic acid	4.7	Phenylalanine	4.1
Cystine	0.3	Proline	6.2
Glutamic acid	17.1	Serine	5.6
Glycine	0.4	Threonine	3.1
Histidine	2.0	Tryptophan	1.4
Hydroxy proline	1.5	Tyrosine	1.0
Isoleucine	4.9	Valine	5.3
Leucine	9.6	Other	11.2
			100.0

aminated and excreted, a smaller quantity might result in equal benefit. Furthermore, if, as seems probable in the human being as well as in the experimental animal, amino acids from an infusion remain available for tissue synthesis for only a few hours at most, then the time schedule for administration becomes particularly important. A large infusion given rapidly 1, 2 or 3 times a day cannot be expected to have the same value as a smaller one spread throughout the 24 hours to permit maximum utilization.

The evidence available gives no indication that when properly handled, amino acid preparations are harmful in any way. Renal function proceeds normally, and in spite of a considerable lag in excretion, large amounts can be handled without difficulty. However, in the presence of renal impairment, whether from disease or from temporary disturbances in circulation or fluid balance no unnecessary load should be placed on the kidney. The smallest amount that permits maximum utilization is desirable, and from the results of the experiments reported above it would appear preferable to administer this slowly over a large part of the day than to follow the more convenient procedure of giving it rapidly in one or two treatments.

Summary and Conclusions

The effects of continuous eight hour infusions of casein hydrolysate have been studied in normal fasting rabbits. At a rate of 1.0 gm. hydrolysate/kg./hr., approximately 5% of the infused material is lost directly into the urine as amino nitrogen. Another 1 to 2% remains in the blood stream during the infusions but is quickly dissipated when the injection is discontinued.

Deamination, as indicated by the accumulation and excretion of urea, increases steadily and proceeds at a rapid rate for approximately four hours after the infusion is discontinued. In all, 60 to 70% of the infused material may appear in the urine as urea, and another 10 to 20% in other forms. A relatively small amount is available for tissue use beyond four hours after the end of the administration.

Although retention of nitrogenous metabolites occurs during infusions at this rate and persists for several hours afterward, renal function is not impaired.

The respiratory quotient during continuous eight hour infusions was found to fall to the level of 0.72 to 0.74. The significance of this is uncertain.

It is suggested that relatively small amounts of complete amino acid mixtures administered continuously might supply the tissues more efficiently than when much larger amounts are given intermittently.

References

1. Elman, R., Maintenance of nitrogen balance by intravenous administration of plasma proteins and protein hydrolysates, Physiol. Rev. **24**:372, 1944.
2. Elman, R., Parenteral Alimentation in Surgery with Special Reference to Proteins and Amino Acids, New York, Paul B. Hoeber, Inc., 1947.
3. Annual Reviews of Physiology, Annual Reviews Inc., Stanford, Calif.
4. Annual Reviews of Biochemistry, Annual Reviews Inc., Stanford, Calif.
5. Peters, J. P., and Van Slyke, D. D., Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1946, vol. 1, chaps. 8-11.
6. Ibid., 1932, vol. 2, p. 547.
7. Albanese, A. A., and Irby, V., Determination of urinary amino nitrogen by copper method, J. Biol. Chem. **153**:583, 1944.
8. Albanese, A. A., and Irby, V., Determination of amino nitrogen of blood filtrates by copper method, J. Lab. & Clin. Med. **30**:718, 1945.

9. Folin, O., Laboratory Manual in Biological Chemistry, New York, D. Appleton-Century Company, 1934, p. 271.
10. Steinitz, K., Determination of urea in blood and urine by Conway units, J. Lab. & Clin. Med. **25**:288, 1939.
11. Lowry, O. H., and Hunter, T. H., Determination of serum protein concentration with gradient tube, J. Biol. Chem. **159**:465, 1945.
12. Van Slyke, D. D., and Meyer, G. M., Fate of protein digestion products in body. III. Absorption of amino acids from blood by tissues, J. Biol. Chem. **16**:197, 1913.
13. Van Slyke, D. D., and Meyer, G. M., Fate of protein digestion products in body. IV. Locus of chemical transformation of absorbed amino acids, J. Biol. Chem. **16**:213, 1913.
14. Friedberg, F., and Greenberg, D. M., Partition of intravenously administered amino acids in blood and tissues, J. Biol. Chem. **168**:411, 1947.
15. Handler, P., Kamin, H., and Harris, J. S., Metabolism of parenterally administered amino acids. I. Glycine, J. Biol. Chem. **179**:283, 1949.
16. Kamin, H., and Handler, P., Metabolism of parenterally administered amino acids. II. Urea synthesis, J. Biol. Chem. **188**:193, 1951.
17. Christensen, H. N., Streicher, J. A., and Elbinger, R. L., Effects of feeding individual amino acids upon distribution of other amino acids between cells and extracellular fluid, J. Biol. Chem. **172**:515, 1948.
18. Smyth, C. J., Levey, S., and Lasichak, A. G., Effects of rate of administration of amino acid preparations on urinary wastage of amino acid nitrogen in man, J. Clin. Investigation **27**:412, 1948.
19. Silber, R. H., and Porter, C. C., Urinary excretion of amino acids and peptides by dogs fed protein hydrolysates or amino acids, J. Nutrition **38**:155, 1949.
20. Elman, R., Time factor in retention of nitrogen after intravenous injection of mixture of amino acids, Proc. Soc. Exper. Biol. & Med. **40**:484, 1939.
21. Geiger, E., Experiments with delayed supplementation of incomplete amino acid mixtures, J. Nutrition **34**:97, 1947.
22. Geiger, E., Role of time factor in feeding supplementary proteins, J. Nutrition **36**:813, 1948.
23. Cannon, P. R., Problem of tissue protein synthesis, Federation Proc. **7**:391, 1948.
24. Leverton, R. M., and Gram, M. R., Nitrogen excretion of women related to distribution of animal protein in daily meals, J. Nutrition **39**:57, 1949.
25. Henriques, V., and Anderson, A. C., Ueber parenterale Ernährung durch intravenöse Injecktion, Ztschr. f. physiol. Chem. (Strassb.) **88**:357, 1913.
26. Eckhardt, R. D., and Davidson, C. S., Rapid injection of solution of amino acids: Note on its clinical tolerance in man, New England J. Med. **239**:164, 1948.
27. Pitts, R. F., Comparison of renal reabsorptive processes for several amino acids, Am. J. Physiol. **140**:535, 1944.
28. Goettsch, E., Lyttle, J. D., Grim, W. M., and Dunbar, P., Amino acid studies: Plasma amino acid retention in hypoproteinemic dog as evidence of impaired liver function, J. Biol. Chem. **144**:121, 1942.
29. Goettsch, E., Lyttle, J. D., Grim, W. M., and Dunbar, P., Renal amino acid clearance in normal dog, Am. J. Physiol. **140**:688, 1944.
30. Christensen, H. N., Peptide wastage consequent to infusion of two protein hydrolysates, J. Nutrition **42**:189, 1950.
31. Lombroso, C., and Ardy, C., Scienza della alimentazione. Sugli autolizzati proteici. II. Modificazioni del metabolismo gassoso in seguito all'introduzione parenterale as orale di autolizzati proteici o di peptoni in cani adulti, Atti accad. nazl. Lincei. Rend., Classe sci. fis., mat. e nat. (8), **5**:257, 1948.
32. Wilhelmj, C. M., and Bollman, J. L., Specific dynamic action and nitrogen elimination following intravenous administration of various amino acids, J. Biol. Chem. **77**:127, 1928.
33. Kriss, M., Comparative study of metabolism of certain amino acids with special reference to respiratory exchange and heat production, J. Nutrition **17**:1, 1939.
34. Bridge, E. M., and Noltie, H. R., Action of adrenaline on respiratory quotient, J. Physiol. **85**:334, 1935.

SPANISH ABSTRACT

Estudios Sobre Metabolismo y Aprovechamiento de las Soluciones de Aminoácidos dadas Intravenosamente

Dado el uso en aumento de varios tipos de soluciones de aminoácidos como una fuente completa de los requerimientos proteicos, los autores emprendieron una serie de experimentos en animales simulando en muchos aspectos las circunstancias que se encuentran en los enfermos con objeto de comprender mas claramente el metabolismo de estas substancias y la manera en que son excretados los productos finales de su metabolismo.

Es indudable que durante la administración de las soluciones de aminoácidos como fuente exclusiva de proteínas se producen balances nitrogenados positivos así como la regeneración de las proteínas plasmáticas cualquiera que sea la vía de administración usada, ya se trate de soluciones cristalinas o de hidrolisados de proteínas completas. Sin embargo, ha sido difícil establecer pautas que marquen la cantidad y horario de administración y como resultado se ha usado un criterio empírico basado en gran parte en la experiencia clínica, apoyándose en el principio de que "si poco es bueno, muchos es mejor."

Los experimentos consistieron en estudiar los efectos de la infusión contínua durante 8 horas de hidrolisados de caseina en conejos normales en ayuno, llegándose a las siguientes conclusiones.

1. Cuando el hidrolisado se administra a razón de 1 gramo del mismo por kilo de peso y por hora, el 5% aproximadamente del material administrado se pierde directamente en la orina como nitrógeno aminado, y el 1-2% permanece en la corriente sanguínea durante la infusión pero se disipa rápidamente cuando se suspende la inyección.

2. Después de que se suspende la infusión, la deaminación del hidrolisado aumenta progresivamente y continúa a un ritmo rápido aproximadamente por 4 horas como lo indica la acumulación y excreción de urea. En total, de un 60 a 70% del material inyectado puede aparecer en la orina como urea y otro 10 a 20% bajo otras formas y una cantidad relativamente pequeña es aprovechable por los tejidos después de 4 horas del final de su administración.

3. Aunque existe retención de metabolitos nitrogenados durante la inyección con este ritmo y persiste por varias horas después, la función renal no se altera.

4. El cociente respiratorio durante las infusiones continuas por 8 horas cayó a niveles entre 0.72 y 0.74, cuya significación es incierta.

5. Se sugiere que cantidades relativamente pequeñas de mezclas completas de aminoácidos administrados continuamente puedan abastecer los tejidos mas eficientemente que cantidades mucho mas grandes dadas intermitentemente.

24 High Street

FURTHER STUDIES ON THE TREATMENT OF CONGENITAL ADRENAL HYPERPLASIA WITH CORTISONE

IV. Effect of Cortisone and Compound B in Infants with Disturbed Electrolyte Metabolism

By JOHN F. CRIGLER, JR., M.D., SAMUEL H. SILVERMAN, M.D., AND LAWSON WILKINS, M.D.
Baltimore

IN PRECEDING papers [1-7] the effect of cortisone on various phases of the syndrome of congenital adrenal hyperplasia has been reported. This paper will, therefore, be limited to a discussion of the treatment of infants with this disease who have an associated abnormality of the salt-regulating mechanism of the adrenal. Although this disorder has been recognized for a number of years, its diagnosis and treatment is often a difficult problem; and in general, the prognosis has been poor. With the advent of cortisone, which is capable of controlling the adrenal overactivity and thus preventing the excessive growth and virilization, the outlook is more encouraging. Accordingly, there is need for greater alertness in recognizing the abnormality and for a better understanding of the disturbed electrolyte metabolism, which is the primary cause of death. This paper is a report of data* accumulated over a 20 month period during studies on three infants with this disease.

Case 1. (A79277) L. U., a white female, was admitted at age of 7 wk., markedly dehydrated, undernourished and in a state of shock. Family history was negative and 3 siblings were living and well. Patient weighed 3.2 kg. at birth, when abnormal genitalia, resembling those of a male with hypospadias, were noted. Vomiting began on 2nd day of life and continued, becoming so severe that patient was readmitted to the local hospital at 18 days of age in a state of collapse. Repeated parenteral administration of Ringer's solution seemed to produce some temporary improvement. Vomiting

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These studies were reported in part at the annual meeting of the Endocrine Society, Atlantic City, June 1951.

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* Methods: The 17-ketosteroids were determined by the Callow, Callow and Emmens technic; after extraction of urine with CCl_4 at room temperature as previously described (Wilkins, L., Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence, Springfield, Ill., Charles C Thomas, Publisher, 1950, p. 54), serum Na and K determinations were made by using a Perkin-Elmer flame photometer. Serum Cl and Co_2 were measured by standard technics.

The Na and K content of the foods were calculated from the values given by Bills, C. E., McDonald, F. G., Medermeier, W., and Schwartz, M. C., Na and K in foods and waters, J. Am. Dietetic A. **25**:304, 1949. The concentrations of Na and K in the diets administered were checked periodically by ashing and determining with the flame photometer. The values found agreed reasonably well with those calculated.

continued, however, and over-all condition was unchanged, so she was transferred to The Harriet Lane Home. She was extremely ill, mottled, irritable and markedly dehydrated. She weighed 0.9 kg. less than at birth. There was no abnormal pigmentation. Genitalia were those usually seen in female pseudohermaphrodites. There was a large phallus measuring 2.7 by 1.3 cm. with a small slit-like opening, representing a urogenital sinus, at its base on the ventral side. Labia majora were partially fused ventrally and resembled a bifid scrotum. No gonads were felt either externally or per rectum. On admission the serum Na was 130 mEq./l., serum K 9.0 mEq./l., serum Cl 112 mEq./l. and serum CO_2 18.3 mEq./l.

Patient was studied intensively over an 18 mo. period. Charts 1, 2, 3 and 4 show changes in urinary 17-ketosteroid (KS) excretion, weight and levels of serum Na, K, Cl and CO_2 during various types of treatment. In all charts, normal ranges are indicated by shaded areas. Intake of Na and K was calculated. Charts 2, 3 and 4 are excerpts from chart 1, overlapping various periods to show more clearly transitional changes occurring with alterations in treatment.

Period A. During 1st 29 days of hospitalization, patient was treated exclusively by addition of NaCl to diet. To maintain a state of clinical well being, it was necessary to increase intake of Na to an average of 125 mEq./l./day. At first, NaCl was given partly parenterally but later, as required amount for symptomatic recovery was determined, it was added to formula, made up so that the total fluid intake was 250 to 300 cc./kg./day. Infant rehydrated rapidly; hematocrit decreased from 42 to 31% and NPN fell from 50 to 18 mg./100 cc. Following this, she gained weight steadily and seemed well. In spite of this fact, the abnormal pattern of serum electrolytes was not corrected, and urinary excretion of 17-KS remained elevated, averaging 3.5 mg./day.

Period B. With the previous period serving as a control for determining effect of cortisone on salt-losing tendency, treatment was begun with cortisone 25 mg. intramuscularly/day, while the high NaCl intake was continued. During this interval of 66 days, patient remained well and showed a steady gain in weight with some tendency to accumulate subcutaneous fat, particularly toward the end of the period. As shown on charts 1 and 2, serum Na and CO_2 rose abruptly to normal levels and remained within this range except for 2 temporary decreases between 20th and 40th days. Serum K did not decrease to normal values until near the end of the period. Within 4 days after cortisone therapy was begun, urinary excretion of 17-KS decreased to less than 0.8 mg./day with an average of 0.44 mg./day and remained at this level.

Period C. At this time all added NaCl was removed from formula, while cortisone, 25 mg. intramuscularly/day, was continued. Although patient showed no untoward symptoms, appetite was diminished, and there was a noticeable change in average daily gain in weight, which showed much greater daily fluctuations (chart 2). It became increasingly evident that cortisone in this dosage was excessive. She developed obesity, with mild hypertension, ranging between $\frac{110\text{–}125}{80\text{–}100}$ and a striking moon face. Growth and osseous development were inhibited and musculature became hypotonic as described elsewhere.[4] There was a fall in serum Na and rise in serum K. No appreciable change in serum CO_2 and Cl occurred. Urinary 17-KS remained unchanged, except during a test period with ACTH 100 mg. given intramuscularly (25 mg. q 6 h $\times$ 4) when output rose to 1.2 mg./day.

Period D. During this period of 70 days, since it was apparent that an excessive amount of cortisone had been given, dosage was reduced from 25 to 5 mg./day given intramuscularly, while formula without added NaCl was continued. Patient became irritable, however, and in a few days was refusing feedings and vomiting. By 6th day, she had lost 400 gm. of weight and was obviously dehydrated; so that it became imperative to institute NaCl therapy. With this illness, serum Na and Co_2 fell to 129 and 149 mEq./l., respectively, and serum K rose to 8.6 mEq./l. There was a temporary increase in 17-KS excretion but this subsequently decreased, without alteration of dose of cortisone. Because it was thought that a mild respiratory infection occurring at this time might have contributed to the disturbance another attempt was made to withdraw added NaCl while patient received the same dose of cortisone. This again resulted in a marked weight loss with symptoms of adrenal insufficiency. However, significant changes in serum electrolytes did not occur because administration of large amounts of NaCl was promptly resumed. Marked fluctuations in weight during this period indicate some of the clinical difficulties encountered following a change from an excessive amount of cortisone to a dose sufficient to control adrenal overactivity, but not the salt-losing tendency. During this

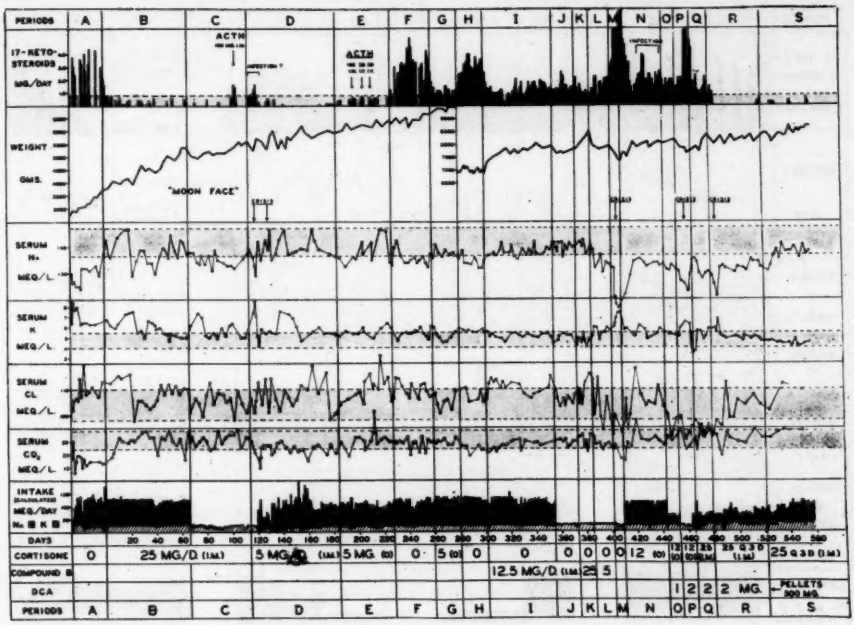

CHART 1. Studies on serum electrolytes and urinary 17-KS in Case 1 during various periods of treatment.

transition, which took approximately a month, patient's appetite remained poor, and vomiting occurred occasionally. Repeated infusions of saline were required while oral intake of NaCl was gradually increased until she was receiving 100 to 110 mEq./day orally. When this adjustment had been made, however, rate of gain in weight again became normal. There was some loss of obesity, and a noticeable increase in strength and activity. Blood pressure returned to normal. After the initial difficulty and readjustment, Na and K generally remained within normal limits and the urinary 17-KS were well below 0.8 mg./day.

Period E. A change to oral administration of cortisone in same dosage of 5 mg./day was accompanied by no essential alteration in patient's clinical or chemical state. Tests were made to determine responsiveness of patient's adrenals to adrenocorticotropic hormone (ACTH) given intramuscularly in doses of 100 mg. and later in 12 hr. continuous intravenous infusions in doses of 25 and 50 mg. No increase in urinary excretion of 17-KS or change in patient's serum electrolytes or clinical condition was encountered.

Period F. To determine whether any permanent change in adrenal function had resulted from 227 days of cortisone therapy, this medication was discontinued, while patient was given the same amounts of added NaCl as in previous period. There was no essential change in her clinical condition during the 32 days without cortisone. Serum Na, however, fell to somewhat lower levels, although serum K and CO_2 showed no significant change. The most interesting finding was the rapid increase in urinary excretion of 17-KS to levels entirely similar to those before any cortisone treatment was instituted.

Period G. Treatment with oral cortisone 5 mg./day was resumed. No change in patient's clinical state was observed, but there was a return of serum Na to normal levels from the slightly low ones of the previous period. There was a rapid suppression of urinary excretion of 17-KS from the high levels of the previous period to an average of 1.2 mg./day, which was distinctly higher than that which had occurred during the previous periods with 5 mg. of cortisone.

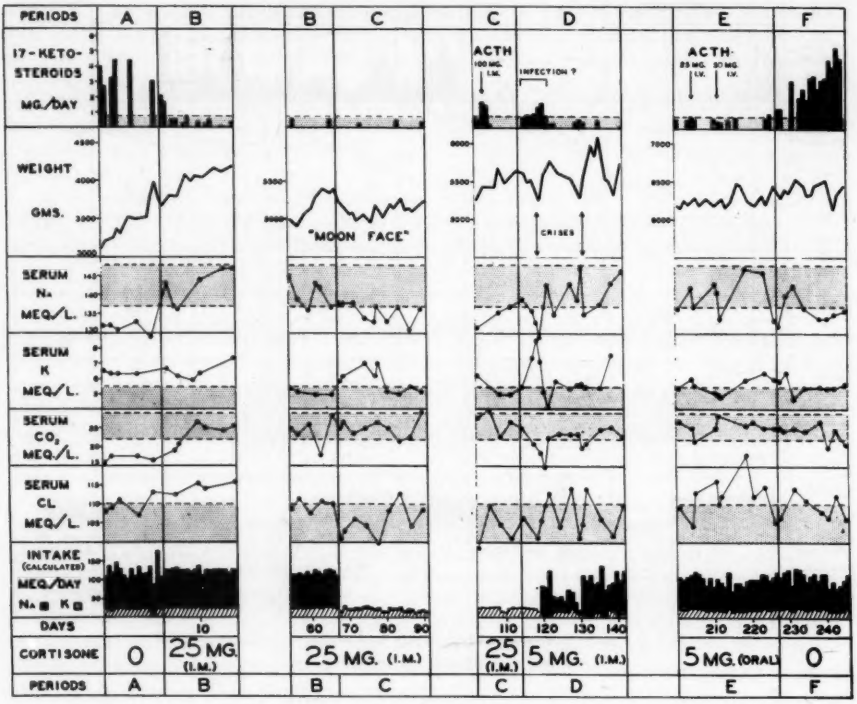

CHART 2. Case 1, showing effects of changes in dosage of cortisone and intake of NaCl on serum electrolytes and urinary 17-KS.

Period H. At this point corticosterone (compound B) was made available. Therefore, cortisone was again discontinued in preparation for the study of corticosterone shown in Periods J-N. Patient remained well although there was again a fall of serum Na, a slight rise of serum K and a rise of urinary 17-KS.

Period I. In this interval of 54 days, patient was maintained on high NaCl intake of previous control period and was given intramuscularly corticosterone 12.5 mg. daily. She remained well and gained weight rapidly. Serum Na and K returned to normal levels. The urinary 17-KS decreased to an average level of 1.3 mg./day, which was higher than had been observed when she was treated with cortisone in smaller dosages.

Period J. Added NaCl was again withdrawn from the patient's feedings while she continued to receive corticosterone 12.5 mg./day. During next 18 days, patient showed no clinical change or alteration in serum electrolyte or 17-KS excretion.

Period K. With no change in NaCl intake, corticosterone was increased to 25 mg. daily intramuscularly to determine if this dose would suppress urinary 17-KS to the previous low levels obtained by cortisone. Following this, there was a rapid increase in weight amounting to 700 gm. in 12 days. This was thought to be due to retention of Na and water in spite of the fact that there was no change in serum electrolytes. By 6th day of treatment, the urinary 17-KS had decreased to 0.9 mg./day. There was insufficient corticosterone available to continue treatment at this dosage for more than 12 days.

Period L. Dose of corticosterone was decreased to 5 mg. daily while patient remained on same diet. Urinary 17-KS increased gradually to 2 mg./day. There was a rapid loss of extra weight which had been gained in the previous period. Serum Na fell to levels of 130 to 132 mEq./l. and K rose to

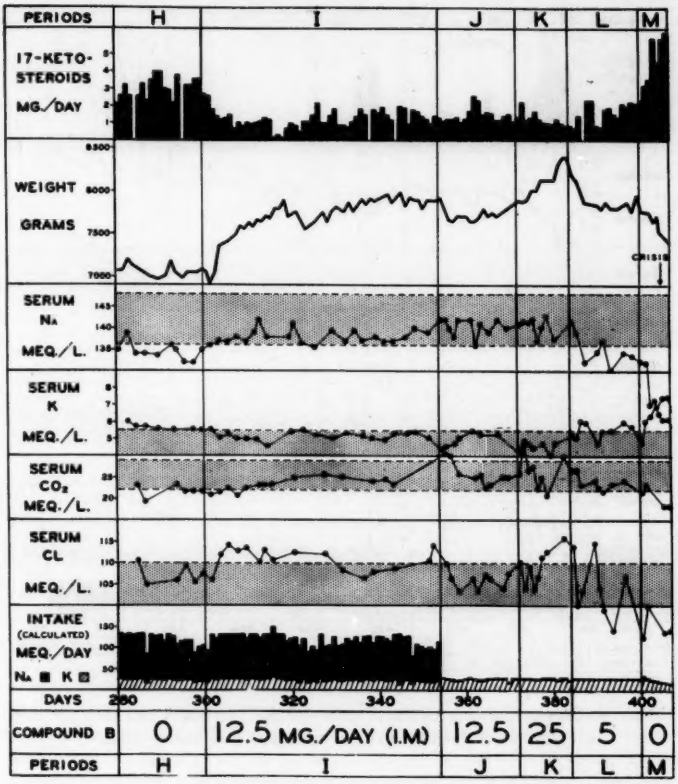

CHART 3. Case 1, showing effects of various doses of corticosterone and changes of salt intake on serum electrolytes and urinary 17-KS.

5.8 mEq./l. In spite of these changes, it was possible to continue the regime with normal Na intake for 16 days without the patient becoming acutely ill or obviously dehydrated. However, progressive loss of appetite, irritability and an appearance of apprehension suggested that a crisis was impending. This was in marked contrast to Period D, when withdrawal of added NaCl during treatment with cortisone 5 mg. intramuscularly precipitated a salt-losing crisis within 3 days.

Period M. With no change in NaCl intake, corticosterone was discontinued. During next 7 days, there was a progressive change in clinical state with loss of appetite, vomiting, marked irritability, increasing oliguria and lethargy. With this, there was a 700 gm. loss of weight. On 3rd day, serum Na fell precipitously and by 7th day serum Na, Co_2, Cl and K were 117, 18.3, 94 and 7.5 mEq./l., respectively. Upon withdrawal of corticosterone urinary 17-KS rose to 6.3 mg./day.

Period N. Treatment was begun with NaCl and cortisone, 12 mg. orally/day. Despite her condition, only 3 gm. of NaCl was given subcutaneously in 1st 2 days since she was able to retain most of formula containing added NaCl 5 gm. Within 2 days, patient was asymptomatic and again retained all of feedings. Ten days elapsed before serum Na returned to values between 132 and 135 mEq./l., a range where it remained for the rest of this period. Serum CO_2, Cl and K showed a similar tendency to return to normal limits although K remained somewhat elevated. Urinary 17-KS fell to an average value of 2 mg./day. Fluctuation in excretion of 17-KS and lack of more marked suppression possibly reflect intermittent bouts of low-grade fever which accompanied a mild respiratory infection during this interval.

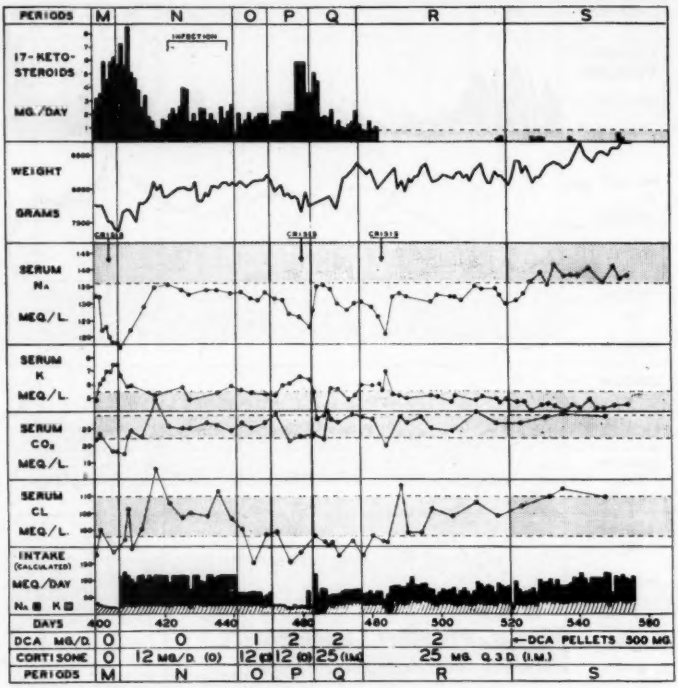

CHART 4. Case 1, showing effects of different doses of DCA and cortisone and changes of salt intake on serum electrolytes and urinary 17-KS.

Remaining periods represent an attempt to adjust treatment with added NaCl, cortisone, and desoxycorticosterone acetate (DCA) preparatory to discharge.

Period O. NaCl intake was reduced to 2 gm. added to daily formula, and DCA 1 mg./day given intramuscularly was begun. Cortisone was continued as before. There was no change in patient's clinical condition and serum electrolytes and urinary 17-KS remained essentially the same.

Period P. DCA was increased to 2 mg./day and as she seemed in good clinical condition, NaCl was omitted to determine if this amount of DCA alone was adequate. In the latter half of this 10 day period, she became ill with marked vomiting and a rise in 17-KS to 5.9 mg./day. Accompanying this, there was a marked fall in serum Na and Cl and rise in K.

Period Q. It was necessary to administer parenteral NaCl in large amounts as feedings were not taken. Cortisone was increased to 25 mg./day intramuscularly and DCA 2 mg./day was continued. During initial 2 days, serum Na rose and K fell to 3.4 mEq./l., probably resulting from the fact that patient had a moderately high Na intake without any dietary K while receiving DCA. On 3rd day, however, she began to take a formula with added NaCl 2 gm. and, thereafter, she recovered symptomatically although serum Na again fell to 130 mEq./l. and serum Cl remained low. Serum K was not significantly abnormal. With increased dosage of cortisone and change to intramuscular administration, urinary 17-KS fell during next 6 days to an average of 1.5 mg./day.

Period R. During this period, cortisone was decreased to 25 mg. every 3rd day and administration of 2 mg. of DCA was continued. An attempt was made to introduce solid foods which at first were taken poorly. Increasing amounts of NaCl were added to formula, but due to the fact that her appetite was finicky, actual Na intake was not increased. At the beginning of this period, there was another unexplained episode of anorexia and vomiting during which serum Na fell and K rose. It is interesting that such an episode was also observed in Case 3 (chart 6—S. K.) where an accompanying rise in 17-KS was observed when a similar alteration in cortisone administration and dosage was

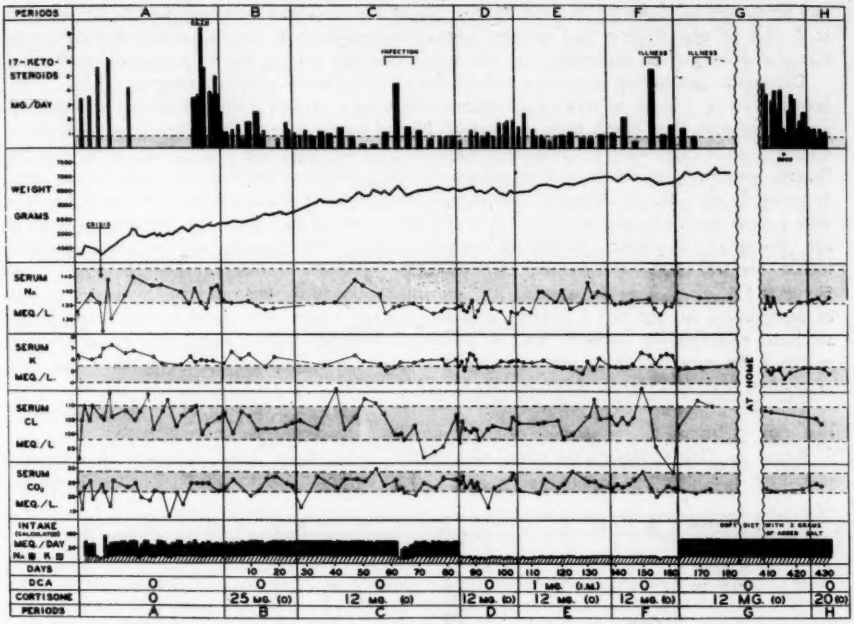

CHART 5. Case 2, showing effects of various doses of cortisone and DCA and changes of salt intake on serum electrolytes and urinary 17-KS.

made. In neither case can a satisfactory explanation be found for this coincidence. She recovered from this when given parenteral NaCl, but serum Na remained below normal while serum K and Cl returned to normal. During most of this period the patient was not kept on the metabolism bed and urine was not collected for 17-KS determination, but at the end it was found that output had decreased to 0.3 to 0.5 mg./day.

In retrospect, it was felt that difficulties in regulating adrenal suppression and electrolyte control during Periods N—Q resulted from a combination of effects. The lack of satisfactory adrenal suppression (as measured by 17-KS) seemed best explained by prolonged low-grade fever with infection in period N and/or the fact that cortisone was administered orally instead of intramuscularly. The relative importance of NaCl therapy was emphasized by the findings observed when simultaneously NaCl intake was reduced and DCA begun in the absence of adequate adrenal suppression by cortisone.

Period S. On 520th day of treatment, four 125 mg. pellets of DCA were implanted in scapular region. Intramuscular injections of cortisone 25 mg. every 3rd day were continued and the same amount of NaCl as before was added to diet. From this time on there was marked improvement. Within 1 wk. serum Na had risen to normal range. Appetite improved so that actual intake of NaCl increased by approximately 25 mEq. (1½ gm.). She began to gain weight in an irregular fashion and showed increased vitality and energy. 17-KS remained well suppressed.

At 21 mo. of age and after 557 days of treatment, much of this time spent on a metabolism frame, patient was discharged. At this time height was 74 cm., the average of 13 mo., weight was 8.7 kg., bone age was between 1 and 2 yr. She had 8 teeth. She was bright, active and playful and was just beginning to walk alone. Parents were instructed to continue intramuscular injections of cortisone 25 mg. every 3rd day and to add NaCl 4 gm. daily to her milk. In case of illness the salt was to be increased.

Case 2. (A81728) F. F., a white female, was first seen at another hospital, at age of 5 days because of abnormal external genitalia. Infant had weighed 4.5 kg. at birth and had been asymptomatic. Family history was reported as negative. Subsequent questioning revealed that 1st and 5th pregnancies

had terminated in stillbirths, and that the 3rd sibling died suddenly after admission to this hospital, at 6 days of age. Autopsy had revealed adrenal hyperplasia with female pseudohermaphroditism. Cause of death was not determined, but one might reasonably assume that it was adrenal insufficiency.

Originally, examination revealed a well developed infant with a phallus measuring 2.4 by 1.3 cm., bound down by 2 bands of skin on the underside forming a slit-like groove, at the end of which was a single opening from which urine was passed. Phallus appeared very much like a hypospadic penis, especially since there were 2 scrotal-like prominences of wrinkled skin partly fused in the midline. Gonads were not palpable. In view of patient's excellent condition and negative family history, with 3 normal living siblings, diagnostic studies were postponed for admission in 6 wk. However, soon after patient was discharged, she began to spit up frequently. With a respiratory infection at 3 wk. of age, she nearly succumbed, developing marked vomiting with diarrhea, and becoming extremely listless. She was treated with penicillin and recovered, although when admitted to The Harriet Lane Home at 7½ wk. of age, she weighed 255 gm. less than at birth, and appeared chronically, as well as dangerously, ill. She was a scrawny, irritable, mottled, sallow, dehydrated infant. There was no abnormal pigmentation. Genitalia were as previously described. Mother stated that during 2nd wk. of life, a few streaks of blood and mucus had been passed through the slit-like opening on underside of phallus. This had cleared spontaneously.

This patient has now been followed for 15 mo. The 1st 7½ mo., during which she was hospitalized, can be divided for the purpose of discussion into 8 periods, as shown in chart 5.

Period A. This 52 day period served as a control, and includes initial regulation on a formula containing additional NaCl, 3 gm. given with a fluid intake of 140 to 180 cc./kg./day. Parenteral

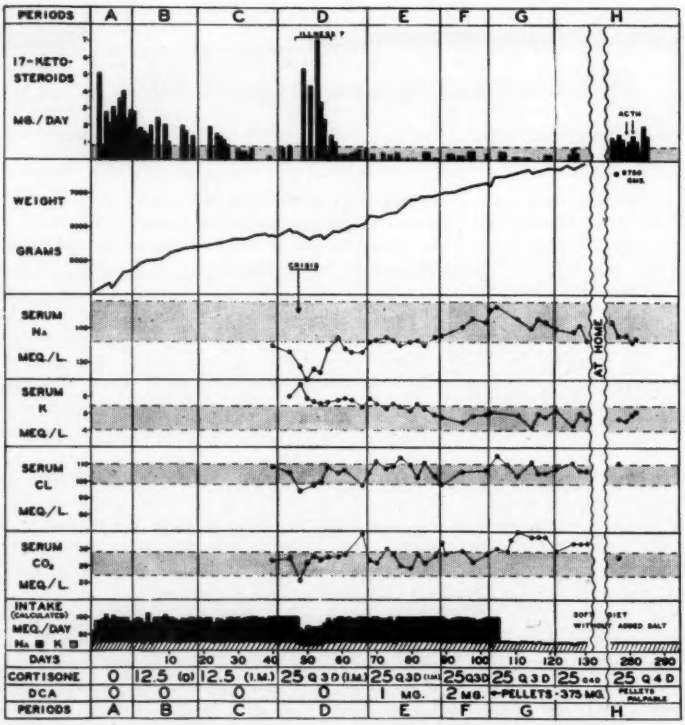

CHART 6. Case 3, showing effects of cortisone, DCA and salt intake on serum electrolytes and urinary 17-KS. Note marked changes in electrolytes and rise of 17-KS which occurred during an illness.

fluids were not necessary. During 1st 6 days on this regime, she did well clinically and showed a progressive gain in weight. Occasional vomiting and spitting, with 2 to 6 loose stools/day observed on admission ceased, and she was no longer irritable. On admission, serum Na and K, done in another laboratory, where 133 and 6.4 mEq./l., respectively. Serum CO_2 was 15.6 mEq./l. and serum Cl 104.6 mEq./l.

After hydration had been restored and patient seemed in good condition added NaCl was omitted as a test of adrenal insufficiency. Within 3 days she lost 180 gm., seemed ill, looked lethargic and refused part of feeding. She went into peripheral vascular collapse at which time the serum Na was 126, K 7.0, CO_2 21 and Cl 94 mEq./l. She was given intravenous and subcutaneous NaCl to which she responded rapidly and then continued with formula containing added NaCl. During remainder of this period, serum Na and Cl were normal. Potassium remained persistently elevated, while serum CO_2 was generally lower than normal. Average urinary 17-KS was 4.2 mg./day.

On 42nd day of this period, a test was made by giving ACTH 100 mg. intramuscularly in 4 divided doses over 24 hr. There was a marked increase in urinary excretion of 17-KS, but no significant change in serum electrolytes or clinical state.

Period B. Treatment was begun with cortisone, 25 mg. orally daily (12½ mg. twice a day), added salt 3 gm. being continued in formula. There was no essential change in clinical condition. She ate well and gained steadily. While changes in serum electrolytes were neither striking nor interpretable, there did appear, however, to be a fall in serum Na. On the other hand, there was an abrupt fall in urinary excretion of 17-KS which averaged 1.5 mg./day during this period. This is slightly higher than average found in the normal infant of this age.

Period C. Since it was felt that a portion of the 17-KS excreted might be a metabolic end product of cortisone administered, the dosage was reduced to 12 mg. orally/day, added NaCl in formula being continued. A change in dosage schedule of cortisone from 2 to 3 times/day seemed to make no difference in its effect. During this 58 day interval, patient remained clinically well except for a mild respiratory infection occurring between 60th and 70th day of cortisone treatment. Prior to this infection, there was a rise in serum Na to normal values although the K remained elevated. With onset of infection, a temporary rise in urinary 17-KS to 4.3 mg./day occurred and a return of serum Na to previous abnormally low values. Although on penicillin therapy the respiratory infection cleared, serum Na and K remained abnormal. A fall in serum Cl occurred during the infection and when added NaCl was omitted by error for 2 days, this was followed by a slow return to normal values, a fact which is not explained. Aside from elevation of urinary 17-KS during the infection, output remained at an average of .95 mg./day throughout this period.

Period D. During this 21 day period, cortisone was continued at same dosage of 12 mg./day, and all added NaCl was removed from formula. Patient did not go into an adrenal crisis, such as occurred within 3 days after added salt was omitted when she was receiving no cortisone (Period A). There were, however, several minor but definite changes in her clinical state. The most striking was her failure to gain weight, with an actual 250 gm. weight loss during this period. Failure to gain was a reflection of loss in appetite, although she did not show any marked alteration in general behavior. There was no significant change in serum electrolyte picture.

Period E. With the previous period serving as a control, the effect of intramuscular administration of DCA/1 mg./day was determined. Over this 33 day interval, there was improvement in patient's appetite, and she again gained weight. Clinically, she seemed entirely normal. Serum Na and K showed a definite tendency to return to normal levels. Urinary 17-KS remained suppressed.

Period F. In this 24 day period, DCA was discontinued, while treatment with cortisone 12 mg./day orally was continued and a formula without added NaCl given as in Period D. While there was a delay of 10 to 14 days, presumably due to continued DCA effect, patient again lost interest in her formula with a resulting loss in weight of 250 gm. A mild illness over a 5 day period, occurring with eruption of first tooth and accompanied by vomiting and fever, probably contributed to this. During this illness, there was a temporary, but marked, increase in urinary excretion of 17-KS to 5 mg./day, and with this a fall in serum Na, Cl and CO_2. Persistence of this change in serum Na and Cl, with elevation of serum K, during the latter portions of this period possibly reflects withdrawal of DCA.

Period G. NaCl 3 gm. were again added to formula and treatment with cortisone was continued as before. There was again a noticeable improvement in appetite and a rather rapid return to average weight gain. This occurred in spite of 6 days of unexplained low grade fever, from 8th to

13th day of this period. Serum electrolytes returned to normal values. It was decided to discharge the patient on this regime since she was doing well and seemed to have a relatively mild adrenal insufficiency. At time of discharge, she was 10¼ mo. old, height age was 6½ mo. and bone age 12 mo. She weighed 7.5 kg.

Patient was readmitted for evaluation 7 mo. later. In the interim she had been well except for 3 upper respiratory infections with fever, vomiting and weight losses of 100 to 300 gm. These had responded well to antibiotic therapy and increased salt intake. Serum electrolytes, determined on a number of occasions during the period at home, had been within normal limits. It had been impossible to collect urine for measurement of 17-KS.

On admission to the hospital, treatment with cortisone 12 mg. orally daily (4 mg. 3 times/day) was continued, and she was given NaCl 3 gm. added to diet. In spite of the fact that she seemed well and showed no evidence of infection, urinary 17-KS fluctuated between 1.0 and 4.5 mg./day, with an average of 2.84 mg./day. Serum Na tended to be slightly low but other electrolytes were normal.

Period H. Because 17-KS did not seem to be suppressed sufficiently, dosage of oral cortisone was increased to 20 mg. daily (5 mg. 4 times/day). This resulted in a decrease of 17-KS to an average of 1.25 mg./day. Serum Na rose to normal levels. Patient was discharged on this treatment. At this time her age was 18 mo., height 73 cm. (average for 14 mo.). Development of different osseous centers was between the 1 and 2 yr. levels. There were 6 teeth. She was bright, active and playful. There was no evidence of progressive virilization.

Case 3. (A83131) S. K. was a 9 wk. old, white infant who was referred because of pseudohermaphroditism and adrenal insufficiency. Family history revealed that first pregnancy had terminated in a full term infant, who died at the age of 2 wk. of undetermined cause.

Except for an abnormality of external genitalia, patient was said to be normal at birth and in good condition. However, because of frequent regurgitation and difficulty in feeding which resulted in dehydration and weight loss, 3 days after mother and patient were discharged it was necessary to readmit patient. In the hospital, although vomiting was inconstant and fluid intake seemed adequate, patient continued to be dehydrated. After a number of studies, including serum Na, K and Cl which were 131, 5.2 and 80 mEq./l., respectively, treatment was begun with DCA, 1 mg./day with addition of NaCl 2 gm. to her diet. This resulted in clinical improvement with a steady increase in weight. Urinary excretion of 17-KS was reported as 2.2 mg./day. After 13 days, DCA was discontinued and patient was maintained on a diet containing 3 gm. of added NaCl. Cortisone was begun with intramuscular injection of 25 mg./day, but this was reduced after several days to 12.5 mg./day. Patient was sent home at 49 days of age and ½ tsp. of salt added to the formula. This was taken readily and she did well as long as cortisone 12.5 mg. was given daily. When cortisone was reduced to 12.5 mg. every other day, appetite became poor, she became irritable, cried a great deal, vomited with increasing frequency, and had some diarrhea. As these symptoms continued, and she again became dehydrated and ill, she was referred for admission. The day prior, she was given DCA 2.5 mg.

On admission examination revealed an irritable, restless infant who weighed 4000 gm. and had no evidence of dehydration. Areolae, labia majora and perianal region showed deep brownish pigmentation. Labia majora were considerably hypertrophied and slightly wrinkled, so that they somewhat resembled scrotal sacs, although gonads could not be felt. Between labia majora there was a large phallus, measuring 2.7 by 1.2 cm. On the ventral surface, demarcated by 2 fibrous cords, was a rather short slit-like groove, at posterior end of which was a small funnel-like orifice from which urine was excreted.

Patient was studied in the hospital for approximately 5 mo.; only that portion of the investigations in which the electrolytes were carefully followed will be reported. (Chart 6—Periods D, E, F, G, H) On admission all hormone therapy was discontinued and patient was given a formula containing additional NaCl 4 gm. She did well on this regime.

Period A. After a period of 10 days, during which average 17-KS excretion was 3.5 mg./day, treatment was begun with cortisone 12 mg. orally (4 mg. 3 times/day), added NaCl being continued.

Period B. There was an abrupt fall in urinary excretion of 17-KS to 1.6 mg./day. Since it was believed that more complete suppression of urinary 17-KS was desirable, after 20 days treatment was changed to intramuscular cortisone, 12.5 mg./day.

Period C. During next 23 days 17-KS fell to levels of 0.2 to 0.6 mg./day. Throughout these 3 periods patient remained in good condition. Weight increased from 4700 to 5700 gm. At the end of this period serum Na was slightly lower than normal, and K moderately elevated.

Period D. For convenience of administration, and because it was believed that less cortisone was necessary, dosage was changed to 25 mg. every 3rd day (average of 8.3 mg./day), and addition of NaCl 4 gm. to diet was continued. During this 26 day period, patient remained well, except for an illness, similar to that described with an identical change in therapy in Period R of Case 1, which occurred 5 days following change of therapy. This illness was characterized by irritability, anorexia and vomiting, and there was a 300 gm. weight loss over a period of 5 days. Physical examination and laboratory studies revealed no cause for this illness. Associated with this disturbance, there was a marked rise in urinary 17-KS and a fall of serum Na and CO_2 with a rise of serum K. Without any change in therapy or diet, 17-KS excretion fell, electrolytes returned to previous levels, and patient recovered. Average excretion of 17-KS, excluding period of illness, was 0.64 mg./day.

Period E. During this 21 day period the effect of intramuscular administration of DCA 1 mg. daily without other change of therapy was determined. Patient remained well. Although there was slight improvement in serum electrolytes, they were not restored entirely to normal. There was no essential change in excretion of 17-KS, which remained suppressed.

Period F. Dosage of DCA was increased to 2 mg./day, without other changes. With this dose serum electrolytes were brought within entirely normal ranges. There was no change in urinary 17-KS.

Period G. As patient was well controlled with DCA, cortisone, and added NaCl, three 125 mg. pellets of DCA were implanted. Within 3 days, she developed marked hypertension, blood pressure rising to 162/94 mm.Hg. Weight increased 250 gm., but no edema was apparent. Serum Na rose but did not exceed normal values. At this time, all added NaCl was discontinued, and there was a gradual return of blood pressure to normal.

Period H. Cortisone was decreased to 25 mg. intramuscularly every 4th day, without alteration in clinical or chemical status. For this reason, it was felt that the pellets of DCA would be sufficient to maintain electrolyte balance without addition of NaCl to diet, provided there was no intercurrent illness. She was discharged on this regime, the parents being advised to give additional salt if she seemed ill or dehydrated at any time.

Four and a half months later, at 1 yr. of age, patient was readmitted for revaluation. In the interim, she had remained well and vigorous. DCA pellets were still palpable. Weight was 9750 gm., height 73 cm. (normal for age). Osseous development was somewhat advanced, a number of 2 yr. centers being present. Six teeth were present. During a study of 12 days, serum Na, K, Cl and CO_2 were within normal limits. Urinary 17-KS fluctuated between 0.5 and 2.0 mg./day with an average 1.23 mg./day. There was a tendency for output to be at higher levels on day preceding cortisone injections. Two tests with 50 mg. and 100 mg. intramuscular ACTH caused no change in urinary 17-KS or serum electrolytes.

She has remained well in the past 3 mo. since returning home.

Discussion

It has been recognized since 1939[8-22] that some infants with congenital adrenal hyperplasia have a disorder of electrolyte metabolism which, if untreated, may cause death from sodium loss and dehydration or from cardiac arrest with hyperkalemia.[20] In the past, treatment with NaCl added to the diet and/or DCA was effective in correcting the electrolyte abnormality and maintaining the patients in comparative health. This therapy, however, did not alter the adrenal overactivity responsible for excessive growth and virilization. It was not until cortisone was used that any form of treatment proved capable of controlling this. With the demonstration that cortisone, administered in small doses, suppressed the abnormal androgenic activity of the adrenal, it became exceedingly important to determine the effect of this steroid on the associated electrolyte disorder. The studies reported were undertaken with this object in mind.

It is apparent that all three of these patients, when not treated, showed clinical and chemical evidences of disturbed electrolyte metabolism. In a short time, without treatment, they became apprehensive and irritable, and lost their appetites. Soon vomiting and weight loss ensued. With these symptoms occurred characteristic alterations in the

serum electrolytes, the Na and CO_2 falling and the K rising. Changes in serum Cl were more variable. In all patients, the administration of large amounts of NaCl controlled the symptoms, and a state of well-being with normal weight gain followed. On the basis of the amount of NaCl required to accomplish this clinical improvement the three cases differed in respect to the severity of the electrolyte disorder, L. U. (Case 1) showing the most severe disturbance and F. F. (Case 2), the least. It is not surprising, therefore, that the former was most sensitive to alterations in therapy and showed the most striking and consistent electrolyte changes. It is noteworthy, however, that despite the clinical improvement on merely giving sufficient NaCl, the administration of NaCl in the amounts given did not in any instance completely correct the abnormal pattern of serum electrolytes.

Evidence for Increased Sodium Retention with Cortisone

The following observations suggest that the administration of cortisone exerted influence in maintaining a normal electrolyte balance:

1. In L. U. (Case 1), cortisone 25 mg./day, given intramuscularly, brought about a restoration of the normal pattern of serum electrolytes which had not been corrected in the preceding period with added NaCl alone (Chart 2—Periods A-B). Later (Periods D, E, G), essentially normal serum electrolytes were maintained with cortisone 5 mg./day, plus NaCl added to the diet.

2. Dosages of cortisone (12 to 25 mg. i. m.) which suppressed the output of urinary 17-KS to amounts normal for age prevented adrenal crises when all added NaCl was removed from the diets, although when the same patients were not treated with cortisone severe crises occurred on the withdrawal of NaCl. For example, in the case of L. U. (charts 1-3) during Period C when the patient was receiving 25 mg. of intramuscular cortisone/day but no added NaCl, she remained well; but when cortisone was reduced to 5 mg./day (Period D) or discontinued (Period M), severe adrenal crises occurred within 6 days, with marked alterations of the serum Na, K, CO_2 and Cl. Similarly, in the case of F. F. (chart 5), the withdrawal of added NaCl during Period A, when no cortisone was being administered, resulted in a severe crisis in 3 days. However, during Periods D and F, while she received cortisone 12 mg./day orally, no ill effects were observed when the added NaCl was omitted from her feedings for 21 and 24 days, respectively. In the absence of added NaCl, intramuscular cortisone in doses of 12 to 25 mg./day prevented serious changes in the serum electrolytes but did not maintain normal levels. Smaller dosages capable of maintaining adrenal suppression, as measured by the urinary 17-KS, did not prevent a crisis, as shown in Period D in the case of L. U. (chart 2).[8]

3. Jailer[7] reported the case of a 2½ yr. old boy with the condition under discussion who required DCA 5 mg. daily while receiving a constant intake of 5 gm. of NaCl in order to maintain electrolyte balance. He found that before treatment with cortisone, withdrawal of DCA resulted in a fall in the serum Na, but on cortisone the 17-KS excretion decreased and it was possible to stop DCA therapy and still maintain serum Na at normal levels indefinitely.

Comparison of the Effect of Corticosterone and Cortisone on Sodium Retention and Adrenal Suppression: In Case 1, a comparison of Periods H to L (chart 3) with similar cortisone Periods A to D (chart 2) shows that corticosterone is more effective in producing sodium retention and somewhat less effective in suppressing the adrenal overactivity. This is, perhaps, as one might have predicted from previous work with corticosterone in Addison's disease.[23]

Possible Action of Cortisone (and Corticosterone) in Preventing Sodium Loss: From the information at hand, at least two ways in which these steroids may influence the electrolyte abnormality in the disorder under discussion must be considered: (1) they may serve as substitutes for deficient "Na-retaining" hormone, and/or (2) they may act by suppressing secretions of abnormal adrenals, which possibly actively cause salt loss.

In some cases of congenital adrenal hyperplasia with disturbed electrolyte metabolism, the zona glomerulosa is absent.[9, 24] This suggests that "Na-retaining" hormone may be lacking, since on the basis of animal experimentation a number of workers believe it is secreted in this zone.[25-28] Furthermore, it has been shown that cortisone and corticosterone are effective in correcting the electrolyte disorder in Addison's disease, where such a deficiency is known to exist.[23, 29] In patients with Addison's disease Thorn et al.[29] reported that cortisone 100 mg. induced a retention of Na and Cl and loss of K equivalent to that of 2 mg. of DCA. More recently, Conn et al.[23] showed that in Addison's disease corticosterone was more effective in controlling the electrolyte metabolism than cortisone but less so than DCA. On this basis, it might seem logical to assume that in some cases of congenital adrenal hyperplasia there is merely a deficiency of "Na-retaining" hormone and that cortisone and corticosterone act only by substituting for this hormone. There are, however, discrepancies which are not easily explained by assuming this relatively simple mechanism for the cause of the electrolyte deficiency.

Several observations strongly suggest the presence of an additional factor which may contribute to the electrolyte abnormality in patients with congenital adrenal hyperplasia:

1. Prior to the use of cortisone in the treatment of this disorder, it was observed clinically that exceedingly large amounts of DCA (up to 5 to 6 mg./day in some cases) and/or NaCl were required to control the salt-losing abnormality, while considerably smaller doses were needed to regulate patients with severe Addison's disease. Darrow[13] suggested that this relative ineffectiveness of DCA in restoring normal concentrations of Na and K in congenital adrenal hyperplasia might be due to overproduction of androgen. Furthermore, the concept that the hormones secreted by abnormal adrenals might actively influence the salt-losing tendency is supported by the authors' finding that, when the adrenal overactivity was suppressed, cortisone and corticosterone which have less sodium-retaining action than DCA in the doses given were effective in controlling the electrolytes.

2. Some years ago, one of the present investigators reported that the administration of ACTH caused a marked sodium diuresis in some patients with congenital adrenal hyperplasia and suggested that the abnormal pattern of steroids secreted may tend actively to promote the loss of Na and cause the electrolyte disorder.[30] Legitimate objections were raised to this interpretation. Subsequently, Jailer[7] reported that in the 2½ yr. old boy, the administration of ACTH for 3 days, while he was receiving DCA 5 mg. and NaCl 5 gm. daily, caused an increase in urinary Na from 70 mEq. to 132 mEq./day and a fall of serum Na from about 133 mEq./l. to 124 mEq./l. The patient lost 400 gm. and looked poorly. While the authors did not have a similar experience in the one patient (F. F.) to whom ACTH was given before cortisone therapy (Case 2—Period A), it is apparent from these studies that during illnesses periods of sodium loss were associated with increased adrenal activity indicated by rises in urinary 17-KS. This is best demonstrated in S. K. (Case 3) during Period D, but was also seen during Periods N and P in L. U. (Case 1) and to a less extent in Periods C and F in F. F. (Case 2). In fact, when the 17-KS were elevated for any reason, there tended to be a fall in the serum Na with less predictable changes in the other electrolytes.

3. Barnett and McNamara,[16] studying potassium and sodium balances in a case of adrenal hyperplasia with electrolyte disturbance, found that withdrawal of DCA and salt therapy caused a loss of intracellular K with no apparent abnormality in renal function. This is different from the reported findings of increased intracellular K and abnormal differential reabsorption of K by the renal tubules in patients with Addison's disease and in adrenalectomized animals.[31] Barnett and McNamara postulated that the difference might be due to the excessive production of androgens or other hormones.

From these observations, it seems probable that the hormones secreted by the abnormal adrenals cause sodium loss. It is not possible, of course, to say whether this results from the production of a specific "Na-losing" factor or from an antagonistic action of some of the steroids secreted against those hormones which normally regulate electrolyte metabolism.

At the present time, therefore, it seems reasonable to conclude that the electrolyte

disturbance in patients with congenital adrenal hyperplasia is not a simple deficiency of the "salt" hormone associated with absence of the zona glomerulosa. It is also necessary to consider the existence of an active principle which in some manner seems to aggravate, to say the least, the salt-losing tendency. On this basis, it might be said that cortisone and corticosterone improved the electrolyte disorder in these patients by a dual action—i.e., by suppression of abnormal adrenal activity and by a specific sodium-retaining effect.

Suggestions Concerning the Therapeutic Management of These Patients: When patients with congenital adrenal hyperplasia show disturbed electrolyte metabolism as evidenced by clinical symptoms or low serum Na, Cl and CO_2 and elevated K, it becomes imperative to correct this disorder as rapidly as possible. Unless this is done, they may go into a state of dehydration with fatal circulatory collapse or die unexpectedly of cardiac arrest due to hyperkalemia, as in the cases reported by Kyle and Knop.[20] The present authors have found the most useful therapy in this situation to be NaCl given in large amounts (4 to 7 gm. daily). Frequently, because of vomiting, it is necessary to give isotonic saline parenterally, but if the patient is taking and retaining feedings to a large extent, this additional NaCl may be added to the 24 hr. formula. By carefully assessing the clinical effects of different amounts of salt, it was found possible to determine the salt and water intake necessary to assure well-being. It should be pointed out, however, that this treatment usually does not correct the abnormality of serum electrolytes and if infection occurs, the difficulty of maintaining normal balance is increased.

After the clinical manifestations of the electrolyte disorder have been corrected, it is next desirable to determine the minimum dose of cortisone required to bring about and maintain suppression of the hyperactive abnormal adrenals in order to prevent excessive growth and progressive virilization. As stated previously this also decreases the amount of supplementary therapy required to obtain normal electrolyte metabolism. During the adjustment of cortisone dosage, the high salt intake is continued. As described previously[3] it is desirable to follow the level of urinary 17-KS as a guide to the suppressive effect of cortisone. To bring about rapid suppression of the adrenals it is advisable at first to give intramuscular injections of cortisone 25 mg. daily for 5 to 10 days. This generally reduces the excretion of 17-KS to levels approaching normal for the patient's age—approximately 1 mg./day for infants under 1 year of age. The dose of cortisone can then be reduced to the minimum amount necessary to maintain this degree of suppression. If excessive doses are given, somatic growth and osseous development may be inhibited and symptoms of Cushing's syndrome may appear. The proper dose for each patient must be determined on the basis of repeated measurements of the urinary 17-KS and the rates of growth and osseous development. Either intramuscular or oral cortisone may be given. The authors prefer, however, the intramuscular route because of the greater uniformity of results and the comparative ease of administration. In Case 3 (S.K.) cortisone 25 mg. given intramuscularly every fourth day proved sufficient. When given orally larger doses are required—probably 12 to 20 mg./day (Case 2), given in 3 or 4 divided doses.

In some patients, treatment with cortisone and a high salt intake may be sufficient to maintain normal electrolyte balance. (See L. U., Periods D and E—chart 1, and F. F., chart 5.) However, in infants with a moderate or severe electrolyte disturbance, it is probably unwise to depend on this therapy alone, and the addition of DCA is recommended. This offers some advantages. The greatest, perhaps, is that there is less need for maintaining a fairly regular intake of NaCl, which may be quite difficult during illnesses when there is loss of appetite and vomiting. If it is decided to add DCA to the therapeutic

regime, it is first necessary to determine the daily intramuscular dose needed when the patient is maintained on the salt intake selected. This may require a month or more. When the intramuscular dose of DCA is known, the number of DCA pellets can be calculated. Each 125 mg. pellet is supposed to be equivalent to a daily dose of 0.5 mg. DCA given intramuscularly. However, it is advisable to administer the amount equivalent to only 2/3 of the calculated intramuscular dose. It should be remembered that during the first week or two following the implantation, before the pellets have become encapsulated, there is a more rapid absorption of the material which may cause temporarily toxic symptoms, such as hypertension or edema. If these occur, the intake of NaCl should be reduced and increased again if necessary.

It must be remembered that the intercurrence of minor infections and other stresses during cortisone therapy often causes an escape from the suppression of adrenal activity, so that the urinary 17-KS rise temporarily to high levels. These escapes are frequently accompanied by a loss of Na, with decrease of serum Na and CO_2 and a rise of serum K. These episodes are manifested clinically by irritability, apprehension, loss of appetite, vomiting and loss of weight. With the refusal of food and at times vomiting, the salt intake is decreased. Unless additional NaCl is given parenterally, rapid dehydration and collapse may ensue. During these episodes it is most important to give additional salt, but it is better not to increase the dose of cortisone unless the elevation of 17-KS continues for a long period.

In concluding, it should be emphasized that these patients must be treated with NaCl and cortisone until full adrenal suppression has been attained before determining the requirements of DCA and NaCl. The reason for this is that less DCA and NaCl are required when the overactivity of the adrenal has been suppressed by cortisone. If, on the other hand, the electrolyte disorder is first adequately controlled by DCA and NaCl, a readjustment will be required after cortisone administration or excessive retention of Na with serious consequences may result. An instance of this was observed by Ordway.[32]

Summary

Three cases of congenital adrenal hyperplasia with disturbed electrolyte metabolism, followed for 14 to 20 months, have been reported in detail.

The effects of cortisone (compound E) and corticosterone (compound B) on the suppression of the abnormal adrenals and on the electrolyte disturbance have been discussed. Cortisone produces more marked suppression of the adrenal overactivity/mg. (as measured by the urinary excretion of 17-KS), but less sodium retention than corticosterone. Both steroids, however, significantly improve the electrolyte abnormality.

The possible mechanism of action of cortisone on the electrolyte metabolism is discussed.

Suggestions concerning the therapeutic management of these patients are offered. The use of adequate NaCl without DCA in the initial treatment is emphasized, since suppression of the adrenal with cortisone seems to alter materially DCA requirement. The final combination of therapy, however, must be decided in each patient individually.

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References

1. Wilkins, L., Lewis, R. A., Klein, R., and Rosemberg, E., Suppression of androgen secretion by cortisone in case of congenital adrenal hyperplasia: Preliminary report, Bull. Johns Hopkins Hosp. **86**:249, 1950.
2. Wilkins, L., and others, Treatment of congenital adrenal hyperplasia with cortisone, J. Clin. Endocrinol. **11**:1, 1951.
3. Wilkins, L., and others, Further studies on treatment of congenital adrenal hyperplasia with cortisone. I. Comparison of oral and intramuscular administration of cortisone, with note on suppressive action on adrenal of compounds F and B, J. Clin. Endocrinol. **12**:257, 1952.
4. Wilkins, L., and others, Further studies on treatment of congenital adrenal hyperplasia with cortisone. II. Effects of cortisone on sexual and somatic development, with hypothesis concerning mechanism of feminization, J. Clin. Endocrinol. **12**:277, 1952.
5. Wilkins, L., and others, Further studies on treatment of congenital adrenal hyperplasia with cortisone. III. Control of hypertension with cortisone, with discussion of variations of type of congenital adrenal hyperplasia and report of case with probable defect of carbohydrate-regulating hormone, J. Clin. Endocrinol. **12**:1015, 1952.
6. Prader, A., Pseudohermaphroditismus femininus mit kongenitaler Nebennierenrinden-Insuffizienz; Günstige Wirkung von Cortison, Desoxycorticosteronacetat und Kochsalz, Helvet. paediat. acta **5**:426, 1950.
7. Jailer, J. W., Recent studies on adrenal hyperplasia, Tr. New York Acad. of Sc., Series II, **13**:262, 1951.
8. Butler, A. M., Ross, R. A., and Talbot, N. B., Probable adrenal insufficiency in infant, J. Pediat. **15**:831, 1939.
9. Wilkins, L., Fleischmann, W., and Howard, J. E., Macrogenitosomia precox associated with hyperplasia of androgenic tissue of adrenal and death from corticoadrenal insufficiency, Endocrinol. **26**:385, 1940.
10. Dijhuizen, R. K., and Behr, E., Adrenal hypertrophy in infants: New clinical entity of neonatal period, Acta paediat. **27**:279, 1940.
11. Thelander, Hulda E., and Cholffin, M., Neonatal cortical insufficiency associated with adrenogenital syndrome, J. Pediat. **18**:779, 1941.
12. Bratrud, T. E., and Thompson, W. H., Congenital hyperplasia of adrenals: Staff meeting, Bull. Hosp. Univ. Minn. **15**:25, 1943.
13. Darrow, D. C., Congenital adrenal cortical insufficiency with virilism, Yale J. Biol. & Med. **16**:579, 1944.
14. van Beek, C., Hyperplasia of adrenal cortex and interrenal intoxication of infants with and without pseudohermaphroditism, Nederl tijdschr. v. geneesk **84**:4507, 1948.
15. Zuelzer, W. W., and Blum, A., Adrenocortical insufficiency in infants with adrenogenital syndrome, J. Pediat. **35**:344, 1949.
16. Barnett, H. L., and McNamara, H., Electrolyte balances in male infant with adrenocortical insufficiency and virilism: Effect of desoxycorticosterone acetate and salt therapy with special references to potassium, J. Clin. Investigation **28**:1498, 1949.
17. Tepper, W., Congenital adrenocortical insufficiency with virilism, J. Pediat. **34**:768, 1949.
18. Gardner, L. I., Sniffen, R. C., Zygmuntowicz, A. S., and Talbot, N. B., Follow-up studies in mixed adrenal cortical disease, PEDIATRICS **5**:808, 1950.
19. Panos, T. C., Female pseudohermaphroditism with hypoadrenia, PEDIATRICS **5**:972, 1950.
20. Kyle, L. H., and Knop, C. Q., Simulation of cardiac disease by adrenocortical failure in infants, New England J. Med. **243**:681, 1950.
21. Knudson, A. G., Mixed adrenal disease of infancy, J. Pediat. **39**:408, 1951.
22. Bierich, J. R., Über das adreno-genitale Syndrom im Kindesalter, Ann. paediat. **177**:241, 1951.
23. Conn, J. W., Fajans, S. S., Louis, L. H., and Johnson, B., Metabolic and Clinical Effects of Corticosterone (Compound B) in Man, Proceedings of the Second Clinical ACTH Conference, Philadelphia, The Blakiston Company, 1951, vol. 1, p. 221.

24. Blackman, S. S., Jr., Concerning function and origin of reticular zone of adrenal cortex: Hyperplasia in adrenogenital syndrome, Bull. Johns Hopkins Hosp. **78**:180, 1946.
25. Deane, H. W., and Greep, R. O., Morphological and histochemical study of rat's adrenal cortex after hypophysectomy, with comments on liver, Am. J. Anat. **79**:117, 1946.
26. Greep, R. O., and Deane, H. W., Cytochemical evidence for cessation of hormone production in zona glomerulosa of rat's adrenal cortex after prolonged treatment with desoxycorticosterone acetate, Endocrinol. **40**:417, 1947.
27. Deane, H. W., Shaw, J. H., and Greep, R. O., Effect of altered sodium or potassium intake on width and cytochemistry of zona glomerulosa of rat's adrenal cortex, Endocrinol. **43**:133, 1948.
28. Jones, I. C., Relationship of mouse adrenal cortex to pituitary, Endocrinol. **45**:514, 1949.
29. Thorn, G. W., and others, Clinical and metabolic changes in Addison's disease following administration of compound E acetate, Tr. A. Am. Phys. **62**:233, 1949.
30. Wilkins, L., Klein, R., and Lewis, R. A., Response to ACTH in Various Types of Adrenal Hyperplasia, Proceedings of the First Clinical ACTH Conference, Philadelphia, The Blakiston Company, 1950, p. 184.
31. Kendall, E. C., Vitamines and Hormones, New York City, Academic Press Inc., 1948, vol. 6, p. 277.
32. Ordway, N. K., Personal communication to the authors.

SPANISH ABSTRACT

Estudios Ulteriores Sobre el Tratamiento de la Hiperplasia Suprarrenal Congénita IV. El Efecto de la Cortisona y el Compuesto B en Niños con Alteraciones del Metabolismo de los Electrolitos

Con el advenimiento de la cortisona, que es capaz en dosis pequeñas de suprimir en forma efectiva la hiperfunción de las glándulas suprarrenales y prevenir así la causa del crecimiento excesivo y virilización de los enfermos con hiperplasia suprarrenal congénita, el tratamiento del trastorno electrolítico asociado, cobra importancia indudable. Por consiguiente hay necesidad de reconocer esta anormalidad y entender mejor el trastorno del metabolismo electrolítico que es la causa primaria de su muerte. Aceptado que la cortisona es esencial para el tratamiento, faltaba por demostrar cual es el efecto de la misma sobre el desequilibrio electrolítico cuando se usa en dosis adecuadas para suprimir la sobre actividad de las glándulas suprarrenales y es el objeto de este trabajo.

Los estudios realizados en 3 casos de hiperplasia suprarrenal congénita con trastorno metabólico electrolítico caracterizado por caida del Na y CO_2 y elevación del K del suero con cambios variables del Cl y clínicamente por ansiedad, irritabilidad, anorexia, vómitos y pérdida de peso, demuestran que la administración de NaCl en la dieta, sin terapeútica hormonal alguna, es capaz de producir un resultado clínico satisfactorio aunque sin corregir por completo el desequilibrio electrolítico. Después de esta fase inicial del tratamiento, que sirvió de control, se ensayaron varios régimenes terapeúticos con cortisona, y en uno de los casos se prescribieron régimenes similares usando corticosterona (compuesto B) en lugar de la cortisona. Durante dichos periódos terapeúticos los enfermos fueron vigilados clínicamente en forma acuciosa y se hicieron determinaciones frecuentes de Na, K, CO_2 y Cl del suero sanguíneo así como de los 17 Ketosteroides urinarios. De estos estudios se concluyó que tanto la cortisona como la corticosterona mejoran en forma significativa el trastorno electrolítico en las dosis pequeñas que se requieren para suprimir la hiperfunción suprarrenal, pero la cortisona produjo mucho mas supresión de dicha hiperfunción por miligramo, medida por la cifra de los 17 Ketosteroides urinarios, con menor retención de Na que la corticosterona.

El mecanismo por el cual estos esteroides mejoran la tendencia a perder sal en la hiperplasia congénita suprarrenal puede ser bien porque substituyan a la "hormona de retención del sodio" que se encuentra en cantidad insuficiente o que actuen suprimiendo las secreciones de las glándulas suprarrenales anormales que posiblemente causen la pérdida activa de la sal.

Las normas terapeúticas que los autores aconsejan hacen énfasis en que los enfermos deben tratarse inicialmente con Na Cl y cortisona hasta que se obtenga la supresión de la actividad suprarrenal y en seguida determinar los requerimientos de acetato de desoscicorticosterona y cloruro de sodio ya que se requiere menor cantidad de estas substancias cuando se ha obtenido dicha supresión funcional.

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STOOL FREQUENCY OF NORMAL INFANTS IN THE FIRST WEEK OF LIFE

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A STUDY of the stool frequency of normal newborn infants was undertaken from two points of view. The first was to ascertain what constitutes normalcy with regard to number of stools per day or more especially with regard to the upper and lower limits for number of stools per day. Incidental to this was an analysis of the pattern of day-to-day variation. The second aspect of the study was to compare the stool frequency of babies on four different feeding regimens in order to ascertain if there were any observable differences that could be related to these methods of feeding.

The management of newborn care on the University Service of the Grace-New Haven Community Hospital has been advantageous for this latter comparison, for the establishment of the rooming-in units[1] has made it possible to observe babies fed on flexible schedules as well as babies cared for in the regular newborn nursery and fed on the conventional four hour schedule. The term flexible schedule feeding as used here is to be considered synonymous with self-demand or ad lib feeding. In addition there has been a considerable number of infants fed at the breast both in the rooming-in units and in the nursery so that it has been possible to compare the stool frequency of babies fed human milk with that of babies fed a cow's milk mixture.

MATERIALS AND METHODS

The stool frequency of 800 infants was analyzed. The groupings were as follows: 200 breast fed on a flexible schedule in rooming-in; 200 bottle fed on a flexible schedule in rooming-in; 200 breast fed in the nursery on a 4 hr. schedule; 200 bottle fed in the nursery on a 4 hr. schedule. Records of babies born on the University Service of the Grace-New Haven Community Hospital from 1946 to 1950 were examined and screened for length of hospital stay and health of the baby. As the required length of hospitalization for postpartum mothers and their newborn babies was shortened in 1948, most of the records analyzed were from the period from 1946 to 1948 in order to insure data for a full 7 days of hospitalization. As the total number of rooming-in mothers who have bottle fed their babies is small, the records for this group have been analyzed through July 1950. (Rooming-in mothers may elect to stay in the hospital longer than the present minimal requirements of 5 days for multipara and 6 days for primipara.) Hospital records were analyzed in all cases. In most cases these were checked with the nurses' daily record sheets which are subdivided by hour for such observations as stools and feeding. In this way avoidance of errors in recording on the permanent record was assured. Babies were excluded from the study only on the basis of ill health. Any baby who became ill in any way during the 1st 6 wk. of life was excluded. Babies born by cesarian section or after difficult delivery were excluded as were those who had difficulty breathing or feeding during the first few days of life. Any baby weighing less than 2500 gm. at birth was excluded. The neonatal health was observed through periodic home visiting by the Pediatric Staff[2] and 6 wk.

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postnatal check-up at the hospital. The milk mixture received by the 400 bottle-fed infants was in all cases a one-half skim milk preparation with 10% added carbohydrate.* The breast-fed babies were screened to eliminate those who received more than minimal amounts of supplementary feedings of the cow's milk mixture.†

For each group of 200 infants and also for the total group of 800 infants, the mean number of stools and the standard deviations from this mean were calculated for each day. The results were then compared statistically.

At the time of compilation of data, graduate nurses who had been supervisors either in the newborn nursery or in the rooming-in units during the years 1947-1950 (inclusive) were questioned individually about the policy for charting stools. They were found to be in close agreeement in their definition of what to record as a stool and in their instruction to student nurses and to rooming-in mothers. (Most mothers in rooming-in keep a "behavior day record" of the baby's activities during the day and record stools according to instructions from the nurses.) The same procedure was followed for nursery and rooming-in infants throughout the period of observation and continues at the time of writing.

A "stool" is recorded each time the diaper is changed and found to contain fecal material in greater quantity than a simple stain or spot. A stain with no solid fecal material smaller than a 50 cent piece is not recorded; neither is a spot smaller than a 25 cent piece with a "tiny dab" of fecal material. (These are approximate measures used by the nurses to explain what they mean by stain or spot.)

If the baby has apparently just had a stool when the diaper is changed, and continues to eliminate during the subsequent 15 min. or so, it is counted as one stool. Babies who are judged by the nurses to be in process of elimination may be left on an open diaper while other infants are attended to. Rooming-in mothers, as well as student nurses, are instructed by the nursery supervisors to give infants time to complete an elimination or, in other words, not to be too quick in putting on a clean diaper when a baby has just had a stool.

The nursery babies are checked for need of diaper change every 4 hr. before being taken to their mothers for feeding. They are not checked after feeding if they are quiet or sleeping. Between feedings, crying babies are checked for need of diaper change more or less promptly according to the census and to the adequacy of nursing coverage. In rooming-in, diapers are changed somewhat more often because the mothers are more quickly aware of the baby's wetting or soiling. On the other hand, the infants may have longer sleeping periods, and sleeping babies are not disturbed for changing.

Results

Table 1 presents the mean number of stools per day for the entire series. The standard deviations are also included in this table, as in dealing with data of this sort the range of normal variation is of greater interest than the actual average value.

The day of delivery was a partial day in many cases and therefore of doubtful significance clinically and statistically. The data for days one through seven were taken from full 24 hour periods. In all subsequent tables and discussion, the day of delivery will be omitted.

It may be seen from examination of this table that the average number of stools per day increased gradually to reach a peak on the fifth day postpartum, and then decreased. The

* The milk mixture given to infants artificially fed was in all instances a partially skimmed milk to which dextri-maltose® was added. Prior to December 1949, the milk mixture was that described by Dr. Grover F. Powers (PEDIATRICS 1:145, 1948). Since December 1949, dalactum® (Mead Johnson & Company) was used. In these milk mixtures 16% of the total calories is in protein, 66% in carbohydrate and 18% in fat. The food was given in mixtures whose caloric value was about 0.8/cc.

† None of the breast-fed nursery babies received supplementary bottle feedings. Eighty-two of the 200 rooming-in breast-fed babies received supplementary feedings on some days. The maximum number of babies on any one postpartum day was 50. The average amount for those 50 was 2 oz. or a group average of ½ oz./day.

TABLE 1

AVERAGE NUMBER OF STOOLS PER DAY FOR TOTAL SERIES OF 800 BABIES ON 4 DIFFERENT FEEDING REGIMENS

Day	DD	1	2	3	4	5	6	7
Mean	1.4	3.2	3.7	4.2	4.3	4.4	4.2	4.0
σ (Standard deviation)	1.22	1.39	1.62	1.90	2.03	1.87	1.79	1.66

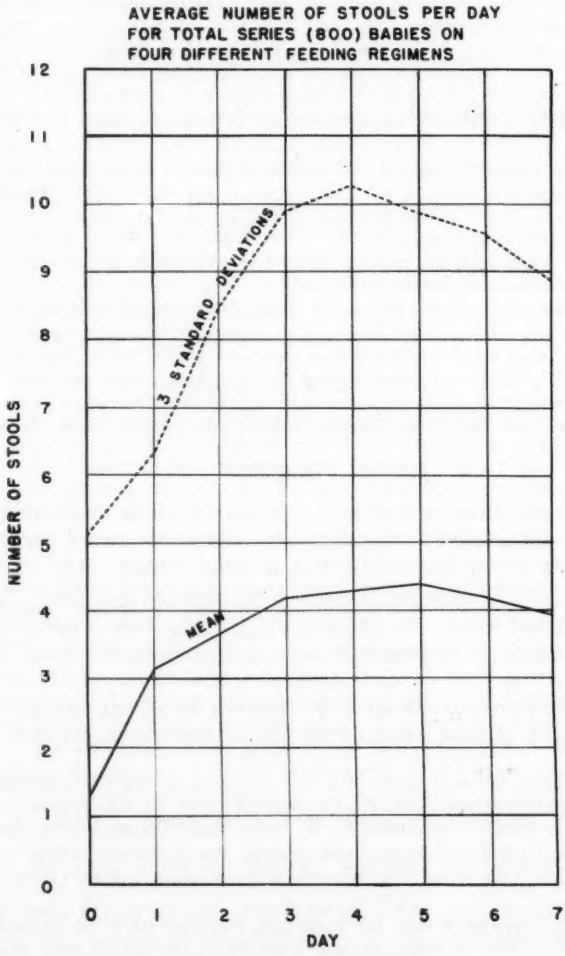

CHART 1

third through the sixth were quite strikingly the peak days with regard to number of stools. This is consistent with other data in the literature. Olmsted and Jackson[3] have shown that the third to the sixth postpartum days were the days of most frequent feedings for breast-fed infants on flexible schedules. Aldrich et al.[4] in their studies of neonatal crying in a hospital nursery found the fourth to the sixth days to be maximum with relation to number of minutes per day that babies cried. This pattern is shown graphically (cf. chart 1). In this chart the mean (continuous line) and three standard deviations (broken line) from the mean have been charted. In this way it was felt that the limits of the normal population could be best portrayed, for a figure three standard deviations above and below a mean will by definition include 99.7% of a normal population. The figures for the standard deviation in addition to representing the limits of a normal population

TABLE 2

ANALYSIS OF MEAN DIFFERENCES (TABLE OF t's) BY DAY FOR TOTAL SERIES OF 800 BABIES ON 4 DIFFERENT FEEDING REGIMENS

Day		1	2	3	4	5	6	7
	Mean	3.2	3.7	4.2	4.3	4.4	4.2	4.0
1	3.2	—	6.18‡	12.0‡	12.8‡	14.0‡	11.6‡	8.64‡
2	3.7		—	6.0‡	6.95‡	8.0‡	5.95‡	3.36‡
3	4.2			—		1.96*		
4	4.3				—			
5	4.4					—		
6	4.2						—	
7	4.0			2.0*	3.05†	3.9‡	2.2*	—

Only those differences which were statistically significant have been presented.
* $p<.05$
† $p<.01$
‡ $p<.001$

give an index of the variability with relation to number of stools on any given day. In this respect it may be seen from an examination of table 1 and chart 1 that as the average number of stools increases and decreases, the variability likewise increases and decreases. The peak days of variability were the third through the sixth days postpartum. These four days then were days not only of greatest number of stools but also of greatest variability. The line for three standard deviations below the mean was on each day the zero line. Frequency distributions were plotted for number of stools on each day. These revealed a quite symmetric distribution, skewed only slightly to the left. There were no sharp breaks at the curves.

In order to determine the statistical significance of this pattern of day-to-day variation in number of stools, an analysis of mean difference by day was performed (t test).[5] Each mean was tested against all others to determine if they differed significantly. This is presented in table 2. This analysis indicates that day-to-day variations at this time of life are highly significant. For nearly every comparison the differences were significant to greater than the one-tenth per cent level of confidence (i.e., there is less than 1 chance in 1,000 that such differences could have occurred by chance). It may be seen from the table that the number of stools on days 2 through 7 were quite significantly greater than the number occurring on the first day. Likewise the values for days 3 through 7 were greater

TABLE 3

ANALYSIS OF VARIABILITY (TABLE OF F'S) BY DAY FOR TOTAL SERIES OF 800 BABIES ON 4 DIFFERENT FEEDING REGIMENS

Day		1	2	3	4	5	6	7
	σ^2	1.94	2.63	3.60	4.12	3.51	3.22	2.74
1	1.94	—	1.356†	1.856†	2.124†	1.809†	1.660†	1.412†
2	2.63		—	1.369†	1.567†	1.335†	1.224†	1.402†
3	3.60			—	1.144*			
4	4.12				—			
5	3.51				1.174*	—		
6	3.22			1.118*	1.280†		—	
7	2.74			1.314†	1.504†	1.281†	1.175*	—

Only those differences which were statistically significant have been presented.
* $p<.05$
† $p<.01$

than the values for day 2. When days 3, 4, 5 and 6, the peak days, were compared with each other, the differences were not significant except that the comparison between the fifth and third days revealed a difference (fifth day greater) at the 5% level of confidence (i.e., 5 chances in 100 that this difference could have occurred by chance). The values for day 7 were significantly smaller than those of days 3, 4, 5 and 6.

In order to determine the significance of the day-to-day changes in variability, the variances on the various days were compared with each other by means of the F test[6] (table 3). This table may be approached in the same way as was table 2. Nearly all the differences were significant to greater than the one per cent level of confidence (i.e., there is less than 1 chance in 100 that such a difference could have occurred by chance), or in other words highly significant statistically. It may be seen that day one was the day of least variability. Day four was significantly more variable than any other day. The variability increased to day four which was the most variable, then decreased to day seven which was less variable than any other days except for days one and two.

TABLE 4A

NUMBER OF STOOLS PER DAY FOR THOSE ELEMENTS OF POPULATION THAT HAD MEAN NUMBER AND GREATER THAN MEAN NUMBER OF STOOLS ON EACH DAY*

Day	1	2	3	4	5	6	7
% of Babies	No. of Stools						
50%†	3.2	3.7	4.2	4.3	4.4	4.2	4.0
25%	4.1	4.7	5.5	5.7	5.6	5.4	5.1
10%	5.0	5.7	6.6	6.9	6.8	6.5	6.1
5%	5.5	6.3	7.3	7.6	7.4	7.1	6.7
1%	6.4	7.4	8.6	9.0	8.7	8.4	7.8
$+3\sigma$	7.4	8.5	9.9	10.4	10.0	9.6	9.0

* These figures represent the values for the upper half of a normal distribution curve.
† 50% is equivalent to the mean.

TABLE 4B

PERCENTAGE OF POPULATION (800 BABIES) THAT HAD NO STOOLS ON EACH DAY

Day	1	2	3	4	5	6	7
% of babies with no stools	2.7	2.6	2.6	3.1	1.9	2.0	1.8

Table 4 was constructed from the previous data in an attempt to present in concise form and in one place the portions of the normal infant population about which there is most clinical controversy. These portions represented those babies who had many stools and those babies who had no stools on any given day. The figures in table 4A then represent the mean figures (50%) and the various portions of the population studies that had greater than the mean number of stools on any given day. It presents, also, the per cent of the population that had no stools on any given day, table 4B. With regard to this latter it may be seen that on any day in the first week of life about 2% of normal babies may be expected to have no stools at all. The figure for three standard deviations (3σ) gives the upper limits of this population. These are the figures that are graphically represented in chart 1. It was felt that percentage representation of the normal population might be more readily useful for clinical comparison. It may be seen, for instance, by reference to table 4 that a baby that has nine stools on the fourth day of life is conforming to the pattern of 1% of a normal population and does not necessarily have diarrhea. Actually in working with the raw data from which these statistical formulations were calculated there were a few babies on all of the peak days (4 through 7) who had as many as 12 to 14 stools in the course of 24 hours. These were all, as stated before, perfectly healthy babies. They ate and gained well. There were never any clinical signs that would indicate any ill effect on the baby of this number of stools. Nor did these numbers of stools persist to create an inconvenience to the mothers once they left the hospital. It should be emphasized that values for three standard deviations and 1%, such as those pre-

TABLE 5

AVERAGE NUMBER OF STOOLS PER DAY FOR 4 GROUPS OF 200 BABIES EACH ON 4 DIFFERENT FEEDING REGIMENS

Day	1		2		3		4		5		6		7	
	M*	σ†	M	σ	M	σ	M	σ	M	σ	M	σ	M	σ
Bottle-fed Rooming-in	3.3	1.47	4.1	1.90	5.0	2.09	4.7	2.20	4.5	1.93	4.1	1.85	3.6	2.08
Breast-fed Rooming-in	3.1	1.27	3.4	1.60	3.7	1.91	4.1	2.26	4.3	2.15	4.1	1.99	3.7	1.60
Bottle-fed Nursery	3.3	1.40	3.8	1.38	4.3	1.49	4.2	1.79	4.4	1.65	4.3	1.52	4.2	1.67
Breast-fed Nursery	3.1	1.32	3.3	1.39	3.8	1.75	4.1	1.80	4.3	1.73	4.2	1.85	4.1	1.39
Total	3.2	1.39	3.7	1.62	4.2	1.90	4.3	2.03	4.4	1.87	4.2	1.79	4.0	1.66

* Mean

† σ—Standard deviation

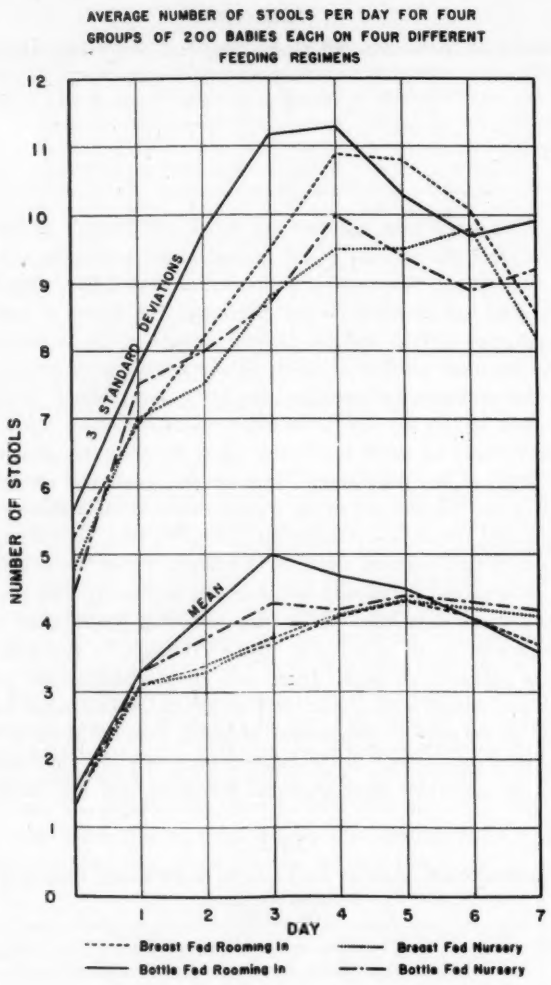
AVERAGE NUMBER OF STOOLS PER DAY FOR FOUR GROUPS OF 200 BABIES EACH ON FOUR DIFFERENT FEEDING REGIMENS
NUMBER OF STOOLS
DAY
3 STANDARD DEVIATIONS
MEAN
Breast Fed Rooming In
Bottle Fed Rooming In
Breast Fed Nursery
Bottle Fed Nursery

CHART 2

sented in table 4A, are quite deviant values statistically. However, the babies were not at all deviant clinically except as regards number of stools. It would seem from these data that rather large numbers of stools and exceedingly small numbers of stools are compatible with normalcy. For this reason the number of stools alone does not indicate a deviation from the normal pattern and the diagnosis of diarrhea in the neonatal period should in all cases be a clinical one, based on a careful examination of the baby and an evaluation of the total behavior rather than a statistical one based merely on the number of stools passed in a given day.

The second aspect of this study involved, as has been stated, a comparison of stool frequency of babies on four different feeding regimens. Two groups of 200 patients each were in the rooming-in units and fed on flexible schedule. One group received breast

milk; the other a cow's milk mixture. Two comparable groups of 200 patients each were in the regular central nursery and were fed every four hours for the duration of their hospital stay. The mean number of stools for each day and their respective standard deviations are presented in table 5. This table is analogous to table 1 and differs only in that the group is subdivided into the above four groups. The same data are presented graphically in chart 2. In these graphs as in chart 1 the mean is represented (bottom group of lines) and three standard deviations from the mean (top group of lines). As in chart 1, three standard deviations above the mean only may be represented, for three standard deviations below the mean was for every day zero.

It may be seen, as would be expected, that the individual groups conform to the pattern of the total group. The mean curves are smooth for all four groups. The standard deviation curves are, however, quite strikingly smoother for the rooming-in babies than for the nursery babies. The clinical significance of this is not apparent. The peak day for the mean number of stools of breast-fed babies regardless of feeding regimen was day four; for bottle-fed babies in rooming-in the peak was on day three; for bottle-fed babies in the nursery the peak day was day six. The peak of variability occurred on day four. In the breast-fed nursery group a secondary peak, actually the maximum, occurred on day six, but for the others this peak was more definite. The curves for the bottle-fed groups rose earlier than these of the breast-fed groups. The bottle-fed groups both in rooming-in and in the nursery tended to have more stools than the breast-fed groups.

Statistical analysis of the mean differences (t test) was performed in order to determine the significance of these apparent differences. The results of this analysis are presented in table 6. The most striking aspect of this analysis was the sparsity of significant differences among the various groups. Out of a possible 32 comparisons, in only seven were

TABLE 6

SIGNIFICANT DIFFERENCES (t VALUES) IN AVERAGE NUMBER OF STOOLS PER DAY AMONG 4 GROUPS OF BABIES ON 4 DIFFERENT FEEDING REGIMENS

Day	1	2	3	4	5	6	7
Bottle-fed Rooming-in / Breast-fed Rooming-in	—	4.09 ($p<.001$)	6.25 ($p<.001$)	2.6 ($p<.01$)	—	—	—
Bottle-fed Nursery / Breast-fed Nursery	—	3.74($p<.001$)	3.03 ($p<.01$)	—	—	—	—
Breast-fed Rooming-in / Breast-fed Nursery	—	—	—	—	—	—	—
Bottle-fed Rooming-in / Bottle-fed Nursery	—	—	3.90 ($p<.001$)	2.4 ($p<.02$)	—	—	—

In each comparison, differences are presented opposite group having greater number of stools.

TABLE 7

SIGNIFICANT DIFFERENCE (F VALUES) IN VARIABILITY OF STOOL FREQUENCY AMONG 4 GROUPS HAVING DIFFERENT FEEDING REGIMENS

Day	1	2	3	4	5	6	7
Bottle-Fed Rooming-in Breast-Fed Rooming-in	1.34 ($p<.05$)	1.41 ($p<.01$)	1.31 ($p<.05$)	—	—	—	1.69 ($p<.01$)
Bottle-Fed Nursery Breast-Fed Nursery	—	—	1.38 ($p<.05$)	—	—	1.48 ($p<.01$)	1.49 ($p<.05$)
Breast-Fed Rooming-in Breast-Fed Nursery	—	1.33 ($p<.05$)	—	1.59 ($p<.05$)	1.55 ($p<.01$)	—	—
Bottle-Fed Rooming-in Bottle-Fed Nursery	—	1.90 ($p<.01$)	1.97 ($p<.01$)	1.55 ($p<.01$)	1.37 ($p<.05$)	1.48 ($p<.05$)	1.55 ($p<.05$)

In each comparison the differences are presented opposite group which was more variable.

the differences greater than one would have expected as a result of purely chance variation.

The first two lines of table 7 involve an estimation of the differences that might be attributable to the use of human or cow's milk. In the first comparison both groups were fed on a self-demand schedule. The only significant differences occurred on days 2, 3 and 4. In the second comparison both groups were fed on conventional four hour schedules. Here the significant differences occurred only on days 3 and 4. All the differences in these two comparisons were highly significant statistically. All of them revealed the bottle-fed babies to have had the greater number of stools on those days. If these differences were related to the actual compositions of the two milks received, it would seem that there would have been differences on every day analyzed. The differences found, as well as the earlier rise of the curves in the bottle-fed babies, seem more logically related simply to the fact that bottle-fed babies receive food on the first day of life, while breast-fed babies await the onset of lactation on the third or fourth postpartum day.

The latter two comparisons are a measure of the effects of flexible schedule feeding as opposed to strict schedule feeding. The third comparison in which both groups were breast fed was most interesting. On no day did statistically significant differences occur. In the last comparison both groups were bottle fed. On days 3 and 4 the ad lib fed babies had significantly greater numbers of stoools than did the schedule-fed babies. These differences may be related to greater food intake on the part of the ad lib babies on these days.

Table 7 presents an analysis of variability (F test) in an attempt to determine which groups were most variable with regard to number of stools and to isolate if possible which

factors were involved. As may be seen on casual inspection, there were many more significant differences than in table 6 where differences in actual number of stools were compared. In the first two comparisons feeding regimen was the constant, and the type of milk consumed the variable. In the first comparison, both groups fed on flexible schedule, the bottle-fed babies were consistently more variable. Significant differences occurred on days 1, 2, 3 and 8. In the second comparison, however, both groups fed on the conventional four hour schedule, the breast-fed babies were on almost every day more variable than the bottle-fed babies. Statistically significant differences were found on only three days. The breast-fed babies were significantly more variable on days 3 and 6, whereas the bottle-fed babies were more variable on day seven. The reversal on day seven is unexplained.*

The relatively consistent greater variability in number of stools of the breast-fed babies over the bottle-fed babies in the nursery and the highly consistent greater variability of the bottle-fed babies over the breast-fed babies in rooming-in might reflect a variability in food intake in the various groups.

The third comparison estimates the influence of flexible schedule in breast-fed babies. Every significant difference indicated the rooming-in babies to be the more variable. The fourth comparison estimates likewise the influence of flexible schedule on bottle-fed babies. Here statistically significant differences occurred on all but the first day. Each difference indicated the rooming-in babies to be the more variable.

It would seem that a definite relationship is hereby established as regards variability in stool pattern. The most variable group was the group of bottle-fed babies in rooming-in. Next most variable were the breast-fed babies in rooming-in. The least variable group were the bottle-fed babies in the nursery. It seems quite probable that the most variable group and the least variable group with regard to number of stools were also the most and least variable groups with regard to food intake. It is also likely that the food intake of breast-fed babies on flexible schedule is more variable than that of babies breast fed on the conventional schedule. It is of interest that breast-fed babies on schedule feeding were more variable than bottle-fed babies on the same scheduling. The parallel of variability in food intake is here hard to avoid. One may dictate quite closely the amount of milk a bottle-fed baby takes at a feeding. This is highly improbable in the case of a breast-fed baby even when the number of minutes at breast are closely limited.

The most striking aspect of these comparisons with regard to both number of stools and to variability, but especially the former, is that the day-to-day differences described earlier in the report are of much greater magnitude than these latter differences attributable to food substance or feeding regimen.

Comments

It appears likely that the number of stools passed by newborn babies is related quite closely with total food intake. In support of this is the fact that the peak days for number of stools coincided with the days previously shown to be maximal with regard to frequency

* The difference on day 7 was significant only at the 5% level of confidence, and therefore there is one chance in 20 that it might have occurred by chance. It is of interest that half of the differences in table 7 are at this level of confidence, whereas nearly all the other comparisons give a much higher degree of assurance. Cf. table 7 ($p < .001$ indicates that there is less than one chance in a thousand that such a result could have occurred by chance).

of feeding. In addition the only significant differences in number of stools between breast-fed and bottle-fed babies in the present series occurred on those days when it might be assumed that lactation had not yet begun. This hypothesis could not be tested because of the nature of the data. Proof would require a specifically designed experiment where the food load was varied and closely measured. Comment has been made relative to the validity of nurses' observations in the central nursery group as to whether the number of stools noted on a hospital chart reflects the stool frequency of the baby or the attitude of the nurse towards observation in general and diaper-changing in specific. The rooming-in group may be considered a check on this possibility, as these babies receive almost constant attention. The fact that significant differences did not occur on any day when the two breast-fed groups were compared seems to insure the validity of these observations.

Summary

The stool frequency of 800 normal infants during the first week of life was studied statistically. The series was composed of 400 infants fed on a flexible regimen, of which 200 were breast-fed and 200 were bottle-fed; and 400 infants fed on the conventional four hour schedule, of which 200 were breast-fed and 200 were bottle-fed. Analyses were made from the points of view of number of stools and variability. The normal pattern was that of rise in both number of stools and variability up to the fifth day and a gradual fall. The peak for both number and variability occurred on days 3 through 6. The range of variation about the mean on each day was quite great and this fact seeemed to militate against a statistical diagnosis of diarrhea in this age group. The comparison among the various groups revealed fewer and smaller differences than the day-to-day comparisons. With regard to number of stools the bottle-fed babies had statistically greater numbers of stools than did the breast-fed babies regardless of feeding regimen, but only during those early days of life when it might be assumed that lactation had not begun. There were no differences between breast-fed babies on the two regimens studied. Bottle-fed babies on self-demand feeding had significantly greater numbers of stools than did those on scheduled feeding on two days. With regard to variability: bottle-fed babies on self-demand were most variable in number of stools per day. Breast-fed babies on self-demand were next most variable and bottle-fed babies on strict scheduling were least variable.

References

1. Jackson, Edith B., and others, Hospital rooming-in unit for four newborn infants and their mothers, PEDIATRICS **1**:28, 1948.
2. Jackson, Edith B., Prophylactic considerations for neonatal period, Am. J. Orthopsychiat. **15**:89, 1945.
3. Olmsted, R. W., and Jackson, Edith B., Self-demand feeding in first week of life, PEDIATRICS **6**:396, 1950.
4. Aldrich, C. A., Sung, C., and Knop, C., Crying of newly born babies. II. Individual phase, J. Pediat. **27**:89, 1945.
5. Fisher, R. A., Statistical Methods for Research Workers, London, Oliver & Boyd, 1941, pp. 106-151.
6. Snedecor, G. W., Statistical Methods, Ames, Iowa, Collegiate Press, 1938, pp. 179-184.

Spanish Abstract

Frecuencia de las Evacuaciones en Niños Normales Durante la Primera Semana de la Vida

Este estudio de la frecuencia de las evacuaciones de niños recién nacidos normales se hizo desde dos puntos de vista. Primero, para obtener un criterio acerca de lo que es lo normal en cuanto al

número de evacuaciones por día o más en lo particular, con respecto al límite mayor y menor del número de evacuaciones diarias. El segundo aspecto del estudio fué el de comparar la frecuencia de las evacuaciones en 4 regímenes de alimentación diferente para comprobar si había diferencia apreciable que pudiera relacionarse con los distintos métodos de alimentación.

En consecuencia, se elaboró estadísticamente la frecuencia de las evacuaciones de la primera semana de la vida de 800 niños normales, los cuales se clasificaron en 2 grupos, el primero estuvo sujeto a un régimen elástico, que lo consideraron como de autodemanda o alimentación ad libitum y lo forman 400 niños, 200 de los cuales fueron alimentados al pecho y 200 artificialmente con botella. El segundo grupo, de 400 niños también, fué alimentado con horario convencional de cada 4 horas, 200 al pecho y 200 artificialmente con botella.

La frecuencia y variabilidad de las evacuaciones para los 2 grupos aumentó progresivamente hasta el 5° día de la vida, a partir de entonces se inició un descenso gradual. El pico más alto tanto en variabilidad como en número ocurrió entre el 3° y 6° días. El grado de variación del promedio del número de evacuaciones de cada día fué muy grande y este hecho parece abogar en contra del diagnóstico de diarrea en esta edad desde el punto de vista estadístico.

El número de evacuaciones de los niños alimentados artificialmente fué estadísticamente mayor que el del grupo alimentado al pecho sin que hiciera la diferencia alguna el que estuvieran con horario o en autodemanda, pero solamente durante aquellos primeros días de la vida en que puede asumirse que no se ha iniciado la lactación. Parece ser pues probable que el número de evacuaciones del recién nacido está relacionado bastante íntimamente con la ingestión total del alimento y además porque los días con pico mas alto del número de evacuaciones coinciden con los días que previamente se demostró que hubo una frecuencia máxima en número de comidas.

No se apreciaron diferencias entre los niños alimentados al pecho ya fuera por horario o por autodemanda, pero los alimentados con botella por autodemanda tuvieron mayor número de evacuaciones en forma significativa que aquellos que se pusieron en horario durante dos dias.

Con respecto a la variabilidad, los lactantes alimentados artificialmente por autodemanda presentaron las variaciones mas pronunciadas en el número de evacuaciones diarias, siguiendo en este aspecto los alimentados al pecho por autodemanda y después los alimentados con botella por horario estricto.

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PRECOCIOUS GROWTH OF SEXUAL HAIR WITHOUT OTHER SECONDARY SEXUAL DEVELOPMENT; "PREMATURE PUBARCHE," A CONSTITUTIONAL VARIATION OF ADOLESCENCE

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GROWTH of sexual hair in a young child suggests the possibility that adrenal tumor or hyperplasia may be causing virilization or that true sexual precocity may be beginning. However, neither of these relatively serious conditions may exist. Approximately 10 years ago workers in the Endocrine Clinic of the Harriet Lane Home became aware of the fact that sexual hair may appear in early life long before there is any other secondary sexual development dependent upon either androgen or estrogen. Although this syndrome has been referred to briefly in textbooks[1-3] as "precocious adrenarche" and "premature pubarche," no detailed studies of a series of cases have been recorded.

The present report is based on a study of 29 children who developed sexual hair before the age of 8 years. It was possible to follow a number of these patients long enough to demonstrate that the condition is a benign variation in the pattern of sexual development and is followed later by normal adolescence. It seems important to bring the findings to the attention of pediatricians who may not be familiar with the syndrome and to discuss its differential diagnosis and probable etiology.

METHODS

Urinary 17-ketosteroids (17-KS) were determined by a modification of the method of Callow, Callow and Emmons previously described,[4] urinary estrogens were measured as the "fluorogenic phenols" by the method of Jailer.[5] Vaginal smears stained by the method of Shorr were interpreted as described elsewhere.[6] The "bone age" was based on the average epiphysial development at all the joints.[7]

CLINICAL AND LABORATORY FINDINGS

In table 1 are recorded the findings in 29 patients, 16 of whom have been followed over a number of years. Some of these children were referred because the presence of sexual hair had suggested the possibility of an adrenal disorder or of sexual precocity, but others had come to the hospital for other conditions and the hair was noted incidentally. Seven patients had varying degrees of mental defect. All but one of the patients were

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† Argentine recipient of the Mead Johnson Fellowship of the Society for Pediatric Research, 1949-1950.

TABLE 1

Series No.	Sex	Age Sexual Hair Appeared (yr.)	Condition on First Examination								Subsequent Sex Development		Condition When Last Examined		Mental Retardation
			Chron. Age (yr.)	Ht. Age (yr.)	Bone Age (yr.)	Sexual Hair			17-KS mg./day	Estrogen γ/day	Age Breasts Developed (yr.)	Age Menarche (yr.)	Chron. Age (yr.)	Ht. Age (yr.)	
						Labial	Pubic	Axill.							
1	F	½	1½	1½	2½	+	+	0	—				1½	1½	*
2	F	½	1	1	—	+	0	0	—				1	1	
3	F	1	1	1	—	+	+	0	—				1	1	
4	F	1	2	2¾	6	+	+	0	1.2				2	3	
5	F	1	2½	3½	—	++	++	0	1.3	5.3					
6	F	1	5	6	—	+	0	0	0.9		—	—	9	10¼	
7	F	4	6	7	—	+++	+++	+++	3.4						
8	F	4¼	5	5½	6	+++	+++	0	1.8				5	5½	*
9	F	5	7¼	9¾	—	++	++	++	2.0		11	12¼	13	(64 in.)	
10	F	5	5¾	7¼	—	+	0	0	—		11	—	11½		
11	F	5	5¼	6½	—	++	++	0	1.4				5¼	6½	
12	F	5	6½	9½	7½	++	0	0	1.6				6½	9½	
13	F	5	7¾	8¼	—	+	0	0	2.3	16	10¾	—	11¼	13	
14	F	5½	6½	9½	7½	+	+	+	0.8	14	—	—	8¼	10½	
15	F	5½	6¾	8¼	—	++	++	0	1.3				6¾	8¼	*
16	F	5¾	6	8	9	+++	+++	+++	3.2		10½	12¼	12½	(66 in.)	
17	F	6	8½	8½	—	++	0	0	—		13	—	13¾	11¼	*
18	F	6	8	8¼	—	++	0	0	—				8	8¼	
19	F	6	10	10	11	++	++	+	9.8	14.9	10+		11¾		*
20	F	6	8	10¼	9	+++	+++	+	3.5				8	10¼	
21	F	6¼	6¾	9½	9	+	+	0	1.1		—	—	10½	13½	
22	F	6½	7½	8¼	9	+++	+++	+	0.8				7½	8¼	
23	F	6¾	8	7	9½	++	0	0	3.2		9½	12	13½	12¼	
24	F	7	7½	10	10	+	0	0	3.3		11	13	15	(69 in.)	
25	F	7	7½	8	9¾	+	+	0	3.2		9½	—	9½	11	
26	F	7	7¼	9¼	9½	+	+	0	2.4	7.2	—	—	9	—	
27	F	7¾	8	9½	9¾	+	+	0	4.0	11.8	—	—	11¼	12¼	
28	F	7¾	9½	11	—	+++	+++	0	—		—	—	11¼	12¼	*
29	M	8	8¼	7¾	9		++	0	3.8		genitalia and testes developed at 12–14 yr.				*

girls in whom the hair appeared before the age of 8 years and in whom there were no other signs of adolescence. Older girls were not included, because after this age the appearance of hair may be merely slightly antecedent to other adolescent changes of normal puberty. One patient was a boy 8¼ years of age.

In girls, hair of coarse crinkly texture usually appeared first on the labia majora, later on the pubis and finally in the axillae. The amount and distribution are shown in the table. It is worthy of note that in only one case was there a moderate degree of generalized hypertrichosis with increased growth of a finer type of hair, particularly over the extremities and back. In none of the cases was there any evidence of true virilization. The clitoris was not increased in size beyond normal limits although in some girls there were prominent preputial folds. None of the patients had acne or deepening of the voice. Most of the children were taller than average and the osseous development was generally 1 to

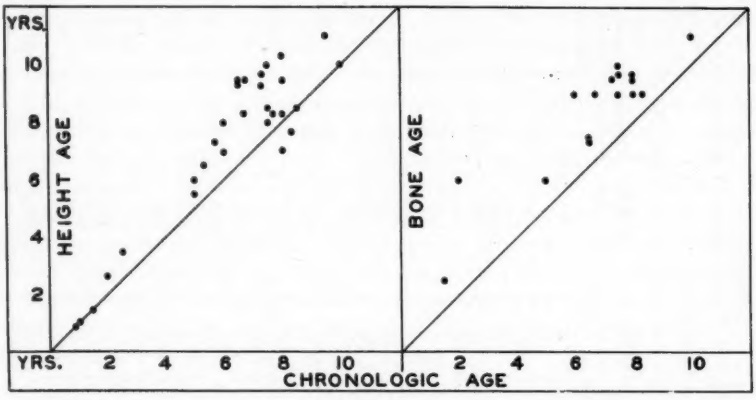

CHART 1. Dots show height-ages and bone ages of patients having precocious growth of sexual hair in relation to average values of children of corresponding ages (diagonal lines).

4 years in advance of the chronologic age (chart 1). The musculature was not unduly developed. Urinary 17-KS were measured in 21 cases. Except in one case the output varied from 0.8 to 4.0 mg./day with an average of 2.15 mg./day. One patient (No. 19), who had developed sexual hair at the age of 6 years, when examined at 10 years of age had an excretion of 9.8 mg. 17-KS/day. However, at this time she was just beginning to show adolescent development of the breasts and nipples and early estrogenic changes in vaginal smears. With the exception of this patient, none of the other girls showed any estrogenic manifestations of adolescent female development at the time they were first examined (9½ years or younger). The nipples were entirely infantile. No mammary tissue was palpable; labia minora were thin and undeveloped; vulval musosa was pinkish-red and glistening, without secretions. Vaginal smears made in 12 girls showed complete absence of estrogenic changes. The output of urinary estrogens was not abnormal in respect to age. In six cases in which they were measured, values between 5 and 16 μg./24 hr. were found, whereas the normal for adult females is from 25 to 50 μg./24 hr.

Thirteen of the girls were subsequently followed until they were 9 to 15 years of age, the period when normal adolescent sexual development may begin. Nine of them have developed breasts and four have had their menarche. As shown in table 2 periods of

from 2½ to 7 years elapsed between the time of appearance of sexual hair and the first development of nipples or breasts was noted. The age when breast development and menarche occurred did not differ significantly from normal. During the span of time when these patients were observed there was no evidence of progressive or excessive virilization. Sexual hair gradually increased over the pubis and in the axillae, but in no case did masculine hirsutism with hair on the chest or face develop. In most cases height continued to be somewhat above the average for age, but the excess over average did not increase with passage of time (table 1). On the other hand, there appeared to be no tendency to premature fusion of the epiphyses with stunted growth.

It is of interest that only one boy has been observed who showed a marked discordance between the time of appearance of sexual hair and the development of other secondary sex characteristics. Pubic hair first appeared when he was about 8 years of age. When he

TABLE 2

Case No.	Age of Onset (yr.)			Present Age
	Sexual Hair	Breasts	Menarche	
6	1	—	—	9
26	7	—	—	9
25	7½	9½	—	9½
21	6¾	—	—	10½
13	5	10¾	—	11¼
27	7¾	—	—	11¼
28	7¾	—	—	11¼
10	5	11	—	11½
16	5¾	10½	12¼	12½
9	5	11	12¼	13
23	6¾	9½	12	13½
17	6	13	—	13¾
24	7	11	13	15

was first examined at 8 years, 6 months, there was an abundant growth of long, coarse, light brown hair over the pubis, but no sexual hair elsewhere. The absence of other secondary sexual development was in striking contrast. The penis was small and slender, measuring 5 x 1.5 cm. The scrotum showed no adolescent changes in size or character of the skin. The testes were of preadolescent size measuring 1.5 x 1. cm. The prostate was not palpable. He was slightly shorter than average, but the bone age was nine years. There was no change in his genitalia until after the age of 12 years when there occurred a gradual development of testes, penis and prostate. When seen later at the age of 15 years, he had matured along normal lines, and the testes measured 4.5 x 2.6 cm.

Differential Diagnosis

Hyperadrenocorticism due to tumor or hyperplasia is the principal disorder from which this condition must be differentiated. Sexual hair may be the first sign of virilization due to adrenocortical tumor. However, in such cases evidences of excessive androgen secretion, such as enlargement of the clitoris or acne, usually appear at the same time as or shortly after growth of pubic hair. Virilization is progressive with rapid acceleration of growth and osseous development, increased musculature, increasing hirsutism of masculine type

and deepening of voice. Marked increase of urinary 17-KS or the presence of large amounts of dehydroisoandrosterone[8] are highly suggestive of an adrenal disorder. If there are no androgenic manifestations except for sexual hair and slightly increased somatic growth and osseous development, and if the urinary 17-KS are not materially increased beyond the normal limit for the age, one should be content to observe the patient at intervals over the next several years. If 17-KS do not increase considerably and there is only slow increase in hair without other evidence of virilization, it is safe to reassure the parents that the condition represents a harmless variation in the pattern of adolescence and that eventually the child will mature quite normally.

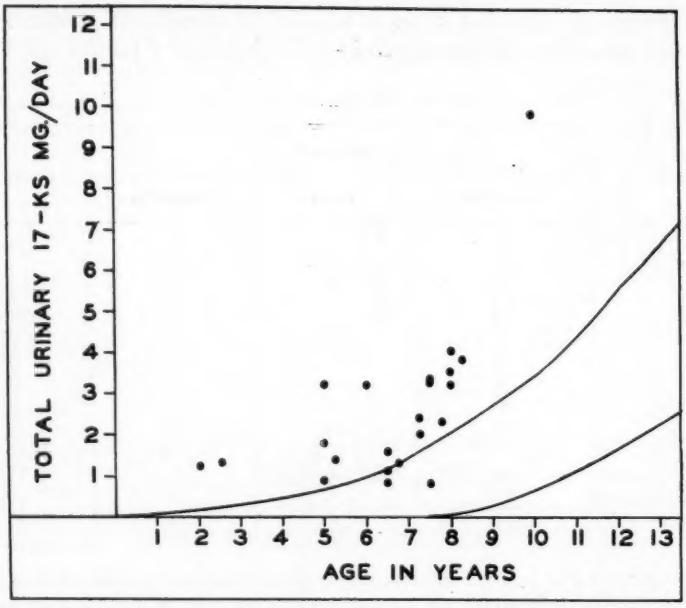

CHART 2. Dots show values of urinary 17-ketosteroids in patients having precocious growth of sexual hair. Lines indicate upper and lower values in normal children.[9]

Sexual precocity in females can be differentiated by the fact that concomitantly with the growth of sexual hair, or shortly thereafter, there is development of nipples, breasts and labia minora, due to secretion of estrogens. Examination of vaginal smears[6] may reveal early estrogenic changes. With sexual precocity of constitutional type or due to intracranial lesions, the penis, prostate and other male sexual organs all develop and the testes enlarge and mature. In the adrenogenital syndrome the testes usually remain immature but other secondary sexual characteristics are advanced.

Although patients with ovarian agenesis develop sexual hair without development of breasts and other sex characteristics dependent upon estrogens, the hair usually does not appear until the age of 12 to 16 years. Patients with ovarian agenesis are usually stunted in statue. This diagnosis depends upon demonstration of increased female sex hormone in the urine.

Etiology

At puberty there is usually a simultaneous increase in secretion of adrenal androgens and sex hormones of the gonads. The latter are controlled by pituitary gonadotropins. It is not known what causes increased production of androgen by the adrenals at adolescence. Variation in the pattern of sexual development described could be due to (1) increased sensitivity of sexual hair follicles to normal levels of androgen present during the preadolescent period or (2) premature increase in secretion of adrenal androgen before the pituitary gonadotropic mechanism becomes activated. In chart 2, 17-KS secretions of these patients are plotted in relation to their age. A comparison with normal levels reported by Talbot[9] suggests that possibly the patients show a slightly increased excretion in relation to age, although this may be due to minor variations in technic. The fact that height and bone age are somewhat above average in most cases, may also be in favor of a slightly increased secretion of androgen. Possibly both these factors play a role. Although 7 of 31 patients had varying degrees of mental defect, it is doubtful whether this had any etiologic role. Early growth of pubic hair probably occurs more frequently than is realized. Children who are otherwise normal are not brought to a physician because of its presence. On the other hand, mentally defective children are brought because of their neurologic disorder and the growth of hair is a concomitant finding. There is no explanation for the fact that the condition is much more frequent in females than in males.

References

1. Talbot, N. B., in Brenneman's Practice of Pediatrics (revised), Hagerstown, Md., W. F. Prior Company, vol. 1, chap. 40, p. 12.
2. Talbot, N. B., Sobel, E. H., McArthur, J. W., and Crawford, J. D., Functional Endocrinology from Birth Through Adolescence, Cambridge, Mass., Harvard University Press, 1952, p. 247.
3. Wilkins, L., Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence, Springfield, Ill., Charles C Thomas, Publisher, 1950, p. 144.
4. Ibid., p. 54.
5. Jailer, J. W., Fluorometric method for clinical determination of estrone and estradiol, J. Clin. Endocrinol. **8**:564, 1948.
6. Wilkins, L.,[3] p. 47.
7. Ibid., p. 35.
8. Gardner, L. I., and others, Urinary dehydroisoandrosterone in hyperadrenocorticism: Influence of cortisone, hydrocortisone and ACTH, J. Clin. Endocrinol., to be published.
9. Talbot, N. B., and others, Excretion of 17-ketosteroids by normal and abnormal children, Am. J. Dis. Child. **65**:364, 1943.

Spanish Abstract

Crecimiento Precoz del Pelo Sexual sin otro desarrollo Sexual Secundario: Una Variación de la Adolescencia, la "Pubertad Prematura"

El crecimiento del pelo sexual en un niño pequeño sugiere la posibilidad de que un tumor o una hiperplasia suprarrenal esté causando virilización o que pueda estar comenzando una verdadera precocidad sexual.

Este informe está basado en el estudio de 29 niños que desarrollaron pelo sexual antes de la edad de 8 años, 10 de los cuales fueron observados durante varios años. Siete enfermos tenían grados variables de defectos mentales. Todas eran niñas con excepción de un niño que tenía 8½ años. El pelo apareció primero en los labios mayores, mas tarde en el pubis y al final, en las axilas. Solo en un caso había hipertricosis generalizada de grado moderado. En ningún de los casos había otros caracteres de virilización verdadera. La mayor parte eran mas altos que el promedio de estatura y el desarrollo óseo estaba de 1 a 4 años mas avanzado en relación con la edad cronológica. El desarrollo muscular era promedio. En los casos en que se dosificaron los 17 Ketosteroides se encontraron dentro

de límites normales con excepción de uno que ya tenía 10 años y se iniciaba su pubertad. Los frotis vaginales de 12 casos no presentaron cambios estrogénicos y en 6 en que se determinaron los estrógenos urinarios se encontraron dentro de cifras normales para su edad.

Trece de las niñas que fueron observadas hasta la edad de 9 a 15 años mostraron un desarrollo sexual adolescente dentro de las variaciones normales.

El diagnóstico diferencial debe hacerse con el hipersuprarrencorticismo debido a tumor o hiperplasia ya que el pelo sexual puede ser el primer signo d virilización en estos procesos, pero la ausencia de secreción excesiva de andrógenos, manifestada por hipertrofia del clítoris y la aparición de acné simultaneamente o poco después, de los signos rápidos de virilización con aceleración rápida y progresiva del crecimiento y desarrollo óseo, aumento de la musculatura, hirsutismo progresivo en tipo masculino y cambio de la voz permite eliminar dichas posibilidades. Un aumento marcado de los 17 Ketosteroides urinarios o la presencia de grandes cantidades de dihidroisoandrosterona son altamente sugestivos de un proceso suprarrenal. En casos de duda, la observación periódica decidirá el diagnóstico. La diferenciación con la precocidad sexual en mujeres se hace porque concomitantemente o poco después se desarrollan los pezones, senos y labios menores y el frotis vaginal revela cambios androgénicos y en los varones por el desarrollo de la prostata, y de sus otros órganos sexuales. En la agenesia ovárica, el desarrollo del pelo sexual es de los 12 a los 16 años generalmente y no hay otras características sexuales y frecuentemente hay detención en crecimiento estatural. El diagnóstico depende de la demostración del aumento en la orina de la hormona estimulante folicular.

Los autores piensan que esta variación del patrón del desarrollo sexual puede ser debida a un aumento de la sensibilidad de los folículos del pelo sexual a los niveles normales del andrógeno presente durante el periódo preadolescente o a un aumento prematuro de la secreción de los andrógenos suprarrenales antes que aparezca la actividad del mecanismo gonadotrópico de la pituitaria.

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RETROLENTAL FIBROPLASIA: CLINICAL OBSERVATIONS

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TERRY[1] in 1942 first brought attention to a bilateral ocular abnormality occurring in premature infants and named it retrolental fibroplasia (RLF). This disease was rare before 1937[2] but its incidence has increased rapidly until now it is a leading cause of blindness.[3] In the United States today RLF is the outstanding complication of survival from extreme prematurity. Although the incidence of RLF in the U.S. is increasing,[2, 4-6] this increase is irregular and varies as much from hospital to hospital as it does from city to city.[2] Terry emphasized the characteristic factor of prematurity, and in a general sense thought that herein the key to the problem might be found.[7]

CLINICAL OBSERVATIONS

Incidence Studies: The high mortality rate of infants born weighing less than 1500 gm. seems to have some bearing on the incidence of RLF. Since two-thirds of all cases of RLF occur in infants born weighing less than 1500 gm.,[5] premature units with high mortality rates will have less RLF than those nurseries with more survivals of the smaller prematures. Therefore, the incidence of RLF reported from various hospitals must be interpreted in terms of their mortality rates, unless only those prematures in the more susceptible weight groups are considered.

Since RLF is now frequently diagnosed in its early active phases,[6, 8-10] some new variables have entered studies of incidence. These errors arise from the fact that the incidence of permanent ocular changes is less than one third of the incidence of the early acute changes,[11-14] which have a marked tendency to regress spontaneously.

Therefore, to be comparable, incidence studies must state whether the disease was in an active phase, or was in the final inactive stage.

Type of Feeding: RLF appears to be a rare disease outside the United States. Mortality figures, comparable with those attained in certain parts of the United States, have been achieved in nurseries in England, Sweden and Denmark, and yet Sweden has but two reported cases,[2] England reports 18 cases[15] and one has been reported in Denmark.[16] Several investigators have pointed out that prematures in Sweden are fed human milk almost exclusively.[14, 17, 18] However, the first four patients with RLF in Sweden were fed cow's milk mixtures.[17] Human milk is used widely in England, although formulae are beginning to be used in some centers there. The premature unit of the Sarah Morris Hospital

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in Chicago uses human milk as the basic diet for their prematures, along with a high fluid intake. The incidence of RLF among their infants is extremely low.[19] This and the European experience has influenced some pediatricians either to continue using or to revert to using human milk for premature feeding.[14] However, the adequacy of formulae for prematures and even its superior qualities in some respects has been demonstrated by many investigators.

To discover whether human milk might protect premature infants against RLF, an experiment was made in the premature unit of the Chicago Lying-in Hospital. Twenty-four infants born weighing from 850 to 1540 gm. were divided into two equal groups. One group was treated differently from the other only in the kind of food offered. The first group was fed nothing but water and autoclaved human milk until a weight of 1800 gm. was attained, and then was isocalorically transferred gradually over a week's time to the formula fed the second group. The second group was fed autoclaved cow's milk with half the cream removed and 10% carbohydrate added. Three patients in each group of 12 developed RLF. No patient receiving human milk had even the first changes of RLF before being transferred to the formula feedings.

Even though this group is small, it seems reasonable to conclude that 100% human milk feeding of the smaller prematures until a weight of 1800 gm. is reached does not prevent RLF developing later.

Fluid Retention: During and immediately following the transfer of 12 infants from human to cow's milk, a sharp increase in rate of weight gain, followed by a resumption of normal weight gain, was recorded. This observation was consistent in all 12 infants, although there was variation in degree of change. At the time of the sharp increase in weight, the general appearance of the infants changed. The contours of the infant were rounded by mild thickening and hardening of the skin, reminding one of the sleek appearance of the infant with mild scleredema. In three infants this process advanced until frank pitting of the scalp and ankles could be demonstrated. Two of these infants were returned isocalorically to human milk feedings. Diuresis and weight loss with disappearance of edema ensued, followed by a resumption, after a few days, of the original daily rate of gain. This experience prompted scrutiny of the infants who had been fed only cow's milk mixtures. By the age of one month these infants commonly had smooth bodily contours from the firm, thick skin referred to before. Two of these infants' feedings were changed isocalorically to human milk. A temporary weight loss with a decrease in smoothness of the body contours, and thinning of the skin was seen to take place. When these infants were returned to the original formula a sharp increase in weight occurred, along with thickening and firmness of the skin.

Some support for these observations on fluid retention is found in clinical and laboratory studies made in 1939 by Gordon and his co-workers.[20] They, too, had seen edema appear in infants transferred isocalorically from human to cow's milk containing similar amounts of carbohydrate, protein and fat. He and his co-workers demonstrated some differences in the usual water and electrolyte retention in these infants. Cow's milk has 4 times the sodium, 2 times the chloride, as well as 7 times the phosphorus and 4 times the calcium content of human milk. Since premature infants have a limited capacity to excrete electrolytes,[20-25] the differences in electrolyte content of the two milks may account for the results of Gordon's study and for the authors' clinical observations. Excessive retention of fluid may be much more common in premature infants fed undiluted cow's milk mixtures than is generally supposed, particularly when salt containing carbohydrate

TABLE 1

INCIDENCE OF PERMANENT BLINDNESS DUE TO RLF AT CHICAGO LYING-IN HOSPITAL IN RELATION TO TYPE OF FEEDING IN INFANTS BORN WEIGHING LESS THAN 1501 gm.

Year	Total Survivals	Pts. w/RLF	Diet and Incidence
1937	15	1	
1938	5	1	"Low electrolyte diet"
1939	12	1	
1940	6	0	
1941	5	0	
1942	9	0	7% incidence (7/103) of RLF (including 1950–51)
1943	9	2	
1944	10	1	
1945	10	1	
1946	3	0	
1946	9	4	
1947	11	5	"High electrolyte diet"
1948	13	6	45% incidence (22/49) of RLF
1949	16	7	
1950	9	0	"Low electrolyte diet"
1951*	10	0	

* First 6 mo.

"Low electrolyte diet" includes human milk and various relatively dilute cow's milk and modified cow's milk mixtures fed in first period. In period of 1950–51, half skimmed cow's milk mixture with 10% added salt-free carbohydrate was used uniformly. During "high electrolyte diet" period, half skimmed milk with 10% added carbohydrate containing 2% sodium chloride was used without exception.

is added to the formula. The incidence of RLF in nurseries with comparable mortality rates is consistently low where human milk is used exclusively,[14, 16–18] and, sometimes, is high where undiluted cow's milk formulae are used.[5, 6, 8–10, 26] An additional contributory factor in the Chicago Lying-in Hospital nursery, where the incidence of permanent blindness due to RLF has been as high as 22 of 49 (45%) infants born weighing less than 1500 gm., may be that the carbohydrate added in 10% ratio to the cow's milk formula contained 2% sodium chloride. (See tables 1 and 2.)

TABLE 2

SODIUM CONTENT OF PREMATURE FOODS (mEq./l.)

Human Milk	Cow's Milk	2% Sodium Chloride	Cow's Milk with 10% Added Carbohydrate Containing 2% Sodium Chloride
6.4	24.4	344	56.4

1650 gm. infant taking 150 cc./kg./day of undiluted half skimmed cow's milk with 10% added carbohydrate has sodium intake of 6.05 mEq./day. Same infant taking same amount of similar formula in which carbohydrate contains 2% sodium chloride has sodium intake of 14.0 mEq./day. On human milk, sodium intake of similar infant would be 1.6 mEq./day.

Transfusion: Blood transfusion for prophylaxis of the anemia of prematurity, a more common practice in recent years, may have some bearing on the etiology of RLF. Since anemia is common in the smaller prematures and does not yield readily to iron or bone marrow stimulants,[27,28] these infants often receive blood transfusions. The anemia is often found shortly before dismissal from the nursery and transfusion then is used to correct it.

To discover if blood transfusion might have any effect on the incidence of RLF, the records of 20 infants born weighing less than 1500 gm. at the Chicago Lying-in Hospital were reviewed. Eight infants had RLF and 12 did not. Although the two groups were fed about the same number of calories/kg., the infants who developed RLF gained at a more

TABLE 3

RELATION OF NUMBER AND SIZE OF BLOOD TRANSFUSIONS TO RLF IN INFANTS BORN WEIGHING LESS THAN 1500 gm.

	Daily Gain gm./kg.	Cal./kg.	No. of Transfusions Given	Av. Vol. Transfusions cc./kg.
RLF (8)	18.5	158	3.3/infant	12.0
Normal (12)	16.4	154	2.0/infant	4.6

Infants with RLF had gained more rapidly than normal infants given similar caloric intakes. Volumes of intravenous blood transfusion given infants later found to have RLF were more than double volumes given normal infants. This was a consistent phenomenon.

rapid rate. Every infant with RLF had been transfused. The number of transfusions given, and the volume in cc./kg. of each transfusion given is significantly greater in the group of infants with RLF than without RLF. None had evidence of sepsis. (See table 3.)

Following the accumulation of these data, the nursery records of 22 patients with RLF born at the Chicago Lying-in Hospital since 1946 were reviewed. All but two of these patients had received blood transfusions before evidence of RLF was discovered.

The premature nursery records of eight blind infants born weighing less than 1500 gm. in another hospital in the same state were then reviewed. All had RLF and each had been transfused. The average number of transfusions given was three. The average volume given with each transfusion was 23 cc./kg. Control studies were not possible.

After these observations had been made in retrospect, ophthalmoscopic examinations were routinely made before and after indicated blood transfusions were given premature infants. Either retinal detachment or severe intraocular bleeding were seen to follow transfusion to four infants with early, ordinarily reversible, vascular lesion of acute RLF.

CASE PRESENTATIONS

Case 1—P, male, was the result of his mother's third pregnancy which was uncomplicated until the 29th wk. when persistent painless vaginal bleeding began. At the 30th wk., labor began suddenly and the infant weighing 1175 gm. was born precipitously in bed. He breathed immediately without aid.

When he was examined in the premature nursery shortly after birth, he was red and vigorous and had no apparent physical abnormality. Feedings were begun on the 2nd day of life with oral glucose solution and then unmodified, autoclaved, human milk. He did well on the feedings and

gained regularly although slowly, regaining his birth weight on the 28th day. In the 2nd week of life a multiple vitamin preparation made water-miscible by homogenization was given him in large dosage: 15,000 units of A, 3000 units of D, 150 mg. of C and an appropriate amount of the B complex. On his 62nd day of life he was given 20 cc. whole blood to maintain his Hgb level at 10 gm./100 cc. (Spencer). On his 68th day of life he weighed 1800 gm. and a gradual transfer of feedings to partially skimmed milk with 10% added carbohydrate containing 2% sodium chloride was begun. Another 30 cc. blood transfusion was given on the 73rd day of life because of anemia, and 20 cc. more blood was given on the 75th day of life. All transfusions were without incident.

On the 75th day of life, a gross, generalized pitting edema of the scalp, arms, hands, legs and feet was apparent and his weight had increased to 2080 gm., a gain of 40 gm./kg./day over the course of 7 days. On the 80th day of life his eyes were examined. He was still grossly edematous. The tactile tensions were normal. The irides were flat. The pupils dilated quickly with homatropine. The media were clear. The retinae were easily seen. The blood vessels were normal in caliber, but mildly wandering in distribution and course. Retinal hemorrhages, exudates and detachments were not seen in either optic fundus. However, both optic discs were obscured by a white fog lying over the surface so that the edges were indistinct and the blood vessels could not be seen to enter the area of the disc.

By the 83rd day of life his blood Hgb. had fallen to 7.7 gm. (Spencer) and on the 3 succeeding days he was transfused with a total of 100 cc. whole blood without incident. The gross generalized edema was less but still present.

On the 91st day of life his eyes were re-examined. The tactile tension of both eyes was increased. Both anterior chambers were then slightly shallow. In the left eye there was a retinal separation elevated to +5 diopters, extending from the ora serrata superiorly almost to the disc. This separation covered 120° of the superior half of the fundus. The optic disc of the left fundus was still obscured by the dense fog, previously described, into which the blood vessels disappeared. The right optic fundus had an easily resolved retinal reflex which was an irridescent green for about 3 disc diameters around the optic nerve head. This green area was elevated over the remainder of the retina about +2 diopters. The blood vessels of the retina had become small in caliber, and disappeared into the obscured region of the optic disc as before. The generalized pitting edema was still present.

On the following day the eyes were examined again. Both pupillary light responses had become sluggish. The retinal separation of the left eye had become complete except for a 120° segment of the nasal quadrants. The retina was elevated to from +5 to +8 diopters, and had several small flame hemorrhages on its surface. The blood vessels had become small in caliber and disappeared as before into the haze over the optic disc. The funduscopic examination of the right eye revealed no real change, except that the retinal elevation in the region around the disc was less, although the green appearance was unchanged. He was discharged from the nursery on the following day.

He was seen at home at age 5½ mo. His left eye occasionally turned in. He could see and fix on even small objects, and followed them well with the right eye but not with the left. The right eye was normal to external and ophthalmoscopic examination. The left eye had a sluggish pupillary response to light. The anterior chamber was slightly shallowed. The red reflex from the retina was elicited, but could not be resolved under the circumstances of the examination. The impression gained was that of an amaurotic left convergent eye and a normal right eye.

His eyes were examined under general anesthesia at age 7 mo. The tactile tension of the right eye was normal. The media were clear and the retina was easily seen. There were no retinal detachments. The region of the macula appears somewhat less brilliant than is usual. Small blood vessels radiated like the spokes of a wheel from 1 to 2 disc diameters from the optic disc. The tactile tension of the left eye was slightly less than normal. The iris had 2 synechiae. The media were clear. Superiorly and inferiorly there were retinal detachments extending from the ora serrata to 3 disc diameters from the optic nerve without apparent retinal tears. These had a green light reflex at +4 diopters and were scantily vascularized. The red reflex around the optic disc was seen best with a −4 diopter lens. The retina where it was not detached was dull and the blood vessels were aberrantly distributed.

Case 2—H, male: The 27 yr. old mother had one spontaneous abortion in 1942, one uneventful term pregnancy in 1947, and this 3rd pregnancy was uncomplicated except for a persistent afebrile

upper respiratory infection beginning at the 20th week and disappearing at about the 24th week. During the 28th week of the pregnancy, labor started spontaneously and progressed uneventfully without sedative to delivery under a low spinal anesthesia.

The infant was born weighing 1060 gm. and breathed immediately without aid. When he was examined in the premature nursery, he was active, his color was good, and the general physical examination was normal with the exception of modest retraction of the sternum and a few scattered rales and rhonchi in the chest. The mild pulmonary disturbance disappeared during the 1st 24 hr. of life. He was never cyanotic. He was then placed on gradually increasing amounts of his own mother's milk. His weight gain was slow but steady. In the second week a multiple vitamin preparation made water-miscible by homogenization was given him in the following dosage: 15,000 units vitamin A, 3,000 units vitamin D, 150 mg. vitamin C and an appropriate amount of the B complex. On the 51st day of life he weighed 1410 gm., and his Hgb. had fallen to less than 10 gm./100 cc. (Spencer). In the following 10 days he was given a total of 75 cc. whole blood divided into 3 transfusions.

On the 66th day of life he weighed 1775 gm. and a gradual isocaloric substitution of cow's milk formula (equal parts of whole milk and skimmed milk with 10% added carbohydrate containing 2% sodium chloride) was begun. Eye examination was made, and revealed no abnormalities. By the end of the week during which this change of formula was made, a gross pitting edema of the scalp, arms, hands, legs and feet had appeared. During this week he gained at the rate of 38 gm./kg./day. On his 72nd day of life, since his blood Hgb. was still less than 10 gm., he was transfused with 20 cc. whole blood. The transfusion was given too rapidly, and the infant had a short cyanotic episode accompanied by fine crackling rales in the chest. The cyanosis lasted less than 5 min. and the crackling rales disappeared the following day.

On the 74th day of life his eyes were examined. The tactile tension of both eyes was greater than normal. The anterior chambers were shallow. The pupillary response to light was sluggish on both sides. After homatropine dilatation, the pupil of each eye was irregular in shape. The vitreous over the right optic disc was filled with white haze obscuring the optic disc and the vessels of the retina for a radius of 1 to 2 disc diameters from the disc. The left disc was partially obscured by a less dense white haze than the right. The light reflexes of the arteries as they passed from the disc to the periphery were obtained only with progressively more plus lenses, until superiorly and inferiorly on the right, and superiorly on the left, a +8 to +10 diopter lens was required to resolve the retinal details and elicit the vascular light reflexes of the retina. This gradual elevation from +1 at the disc to +10 diopters at the periphery was actually a series of successively higher mounds, each with a dip before the next rise. Nasally and temporally in each eye, this elevation of the retina was less marked or absent. A diagnosis of bilateral partial retinal separation of acute retrolental fibroplasia was made. An isocaloric change of feedings to unmodified autoclaved human milk was immediately instituted as treatment. While he took these feedings, his edema steadily lessened.

On the 82nd day of life, 8 days after the retinal detachments were found and 10 days after the cyanotic episode associated with rapid blood transfusion, his eyes were examined a fourth time. The tactile tension seemed less than before, and the anterior chamber was deeper. The pupillary reaction to light was still sluggish, but present. The pupils dilated irregularly as before. The vitreous of both posterior chambers was still mildly hazy, but nowhere completely obscured the retina except immediately over both optic discs, neither of which could be seen in detail. At this examination the vascular light reflexes were obtainable in all quadrants of both eyes with a 0 to +1 diopter lens. The vessel calibers seemed less than normal, particularly of the arteries. On this day no signs of abnormal fluid retention were present, except for thickening of the skin. He weighed 2420 gm., having gained only 11 gm./kg./day over the 10 day period on human milk.

Five days later, on the 87th day of life, his eyes were unchanged, and he was discharged from the premature nursery to his mother who was to nurse him.

At age 6 mo. his eyes were re-examined. At this time he followed small objects with either eye. The tactile tension was not increased. The irides were flat. The pupils actively responded to light, and dilated regularly with 2% homatropine—10% neosynephrin. The media were clear. The retinal light reflex was best seen with a −1 to −2 diopter lens. No abnormalities of the retinae were found in the right or left fundus except for mild irregularity in the course of the blood vessels in the areas of previous retinal detachment. The retinal sheen seemed normal except in the region of the right macula, where the usual foveal reflex could not be found.

Discussion

Some advances have been made recently in the understanding of the pathogenesis of retrolental fibroplasia. There is now general agreement among the various investigators that the disease develops after birth in eyes without apparent congenital malformations.[6, 8–10, 29] The first observable changes are vascular, and occur with "alarming commonness" in infants born weighing less than 1500 gm.[11–13] These changes are vascular engorgement, usually more marked in the venous system, followed by tortuous changes in the courses of the blood vessels with mild to severe bleeding into the retina or vitreous. Then retinal edema and clouding of the vitreous far in the periphery of the fundus and the region of the disc are seen. Myopia develops during this stage. Whether this myopia is due to elongation or to index changes is not yet known. These early changes regress in about 60% of infants developing them, and few signs of retinal disease remain.[8–13, 29] The next two steps are the culminating insults that produce the permanent damage originally recognized as retrolental fibroplasia. The retina detaches locally, usually far in the periphery, the detachment spreads, and the retina billows forward toward the lens. This retinal separation may also reverse, and the retina may reattach itself and be left with varying degrees of damage. Or the blood vessels of the detached retina may atrophy and gliosis and fibrosis begin to produce membrane formation. If the detachment is complete, the classical retrolental scantily vascularized greenish-white mass is produced. If the detachment only partly reattaches, or was never complete, a retinal fold, or septum, or stalk may result and represent an incomplete form of retrolental fibroplasia. The studies of Owens and Owens,[6] Heath,[8] Reese[9] and Unsworth[10] are agreed that it is often difficult to differentiate in the end stages, after all activity has ceased, the acquired from the congenital eye lesions in the last group mentioned—particularly the retinal "dysplasias," stalks and folds.

These retinal changes characteristically occur against a backdrop of extreme prematurity. The frequency with which vascular engorgement and tortuosity, and even retinal edema, are seen in the smaller premature infants, suggests a borderline abnormality of physiology. If the patient is fortunate, these borderline abnormalities may regress without harm. If not, some permanent form of RLF may appear.

There is abundant evidence for lack of the usual adrenal cortical responses to stress in premature infants.[30, 31] Similarly, varying degrees of water and electrolyte retention are common in premature infants. The latter may be due to primary and secondary renal limitations in ability to excrete electrolytes,[21–24] particularly when the diet contains a high concentration of electrolytes.[20, 25]

A commonly recommended premature infant diet has between 3 and 9 times the electrolyte content of human milk.[15, 32, 33] In Sweden, where human milk is used almost exclusively for prematures, it is of interest to note that the first four infants with RLF who were born there had been given a cow's milk formula.[17, 18] RLF has developed in an infant fed only human milk, but this infant had sepsis in the neonatal period.[16] Infants fed low electrolyte diets, and having similar renal capabilities, would not be expected to retain excessive amounts of water and electrolytes. This idea is supported by the clinical and laboratory observations of Gordon et al.[20] as well as the present study.

The investigation of Mallek and Spohn,[34] as well as the present study, indicates an association between blood transfusion and a high incidence of RLF. Intravenous blood transfusion has become common practice in recent years, and in some premature units is almost routine in the smaller infants. Woodbury, Robinow and Hamilton[35] demonstrated

in 1938 that the premature infant has poor presso-receptor responses, and in many respects may be regarded as a presso-receptor denervated animal. Guyton et al.[36] demonstrated in presso-receptor denervated dogs that blood transfusion produces a temporary hypertension. Since the premature has poor presso-receptor activity, he, too, would be expected to have hypertension with a large blood transfusion. The principal remaining means of compensation is reduction of the circulating blood volume by passage of fluid into the extracellular space. The extracellular fluid space may already be greatly expanded in some premature infants. Evidence of this overfilling is easily seen in the retina[6,8] as well as in the bodily configuration and cutaneous changes of these infants. The pressure disturbance brought about by transfusion may be sufficient to precipitate retinal detachment which progresses to irreversible RLF in some infants.

The effect of ACTH on the renal and cellular metabolism of water and electrolytes, as well as on fibroblastic and neovascular tissue activity, may well be operative in infants with the early retinal detachment stage of RLF. The spontaneous reattachment of the retina in Case 2, an edematous premature infant in whom a diuresis was "induced" by a low electrolyte (human milk) diet, may be of some significance. Certainly more is involved in the dramatic reversal of a process causing retinal detachment than inhibition of fibrosis and new vessel formation. An active process restores the normal relationships of the retina and its blood vessels. The primary effect of ACTH on the premature with early retrolental fibroplasia may be induction of a water and sodium diuresis and redistribution of retained electrolytes and water.[30,37]

It is not possible either to produce or to maintain the vascular changes reported in the eyes of kittens without both edema and large blood transfusions.[38] Some similarities exist between the retinal changes of the kitten studies and of Reese and Blodis' early case of RLF,[9] as well as the histologic changes observed by Heath[8] in his patient. Both the human and animal eyes have retinal edema, and engorgement of the retinal and periorbital vessels. Both have capillary hyperplasia and inflammatory cell infiltrations in the retina. The infants reported by Reese and Blodi and by Heath have vascular budding through the retina into the vitreous. This is not present in the kittens. However, the kittens' eyes have vascular budding from the irides, as does the patient of Reese and Blodi. No further similarities exist, since the infant had no embryonic vascular system remnants, and the kittens' eyes in question had a well developed hyaloid artery and tunica vasculosa lentis.

Much of the hypothesis proposed cannot be supported adequately by existing laboratory evidence. However, in view of the great gaps in our knowledge of the premature infant, it seems justifiable to forward these speculations based on clinical evidence given support by a single animal study.[38] Confirmation of many of the fundamental assumptions embodied in the hypothesis demands detailed laboratory study in widely separate fields of investigation. Even so, clinical testing of these ideas by various investigators interested in the problem of RLF can rapidly show the fallacy or validity of this "physiologic" approach.

Summary

Retrolental fibroplasia is a postnatally acquired disease. The basic pattern for the disease is present in the majority of premature infants born weighing less than 1500 gm.

A relationship between the electrolyte content of the diet, and fluid retention can be established in small premature infants. A relationship between large blood transfusions

and an increased incidence of RLF is presented. Exclusively human milk diets, fed until a weight of 1800 gm. is achieved, do not prevent RLF developing later in infants born weighing less than 1500 gm. ACTH may exert its temporary influence on RLF by its diuretic effect on water and salt metabolism in the premature infant.

Two factors, formulae of high electrolyte concentration and blood transfusion, may overload the capacities for physiologic adjustment of the smaller premature infant, and lead to RLF. A direct relationship between the development of RLF and blood transfusion during a period of water and electrolyte retention is reported.

The practice of feeding high electrolyte formulae, and excessively large blood transfusion for anemia may be responsible for the remarkable variation in incidence from hospital to hospital, the variation in incidence even in the same hospital, and the increasing incidence of RLF in premature infants following the introduction of these practices.

References

1. Terry, T. L., Extreme prematurity and fibroblastic overgrowth of persistent vascular sheath behind each crystalline lens, Am. J. Ophth. **25**:203, 1942.
2. Kinsey, V. E., and Zacharias, Leona, Retrolental fibroplasia, J. A. M. A. **139**:572, 1949.
3. Krause, A. C., Blindness in premature infants, with special reference to retrolental fibroplasia, Texas Rep. Biol. & Med. **9**:46, 1951.
4. Krause, A. C., Congenital encephalo-ophthalmic dysplasia, Arch. Ophth. **36**:387, 1946.
5. Hepner, W. R., Krause, A. C., and Nardin, Helen E., Retrolental fibroplasia: Study of 66 cases, PEDIATRICS **5**:771, 1950.
6. Owens, W. C., and Owens, N. U., Retrolental fibroplasia in premature infants, Am. J. Ophth. **32**:1, 1949.
7. Terry, T. L., Fibroplastic overgrowth of persistent tunica vasculosa lentis in premature infants: Etiologic factors, Arch. Ophth. **29**:54, 1943.
8. Heath, P., Retrolental fibroplasia as syndrome: Pathogenesis and classification, Arch. Ophth. **44**:245, 1950.
9. Reese, A. B., and Blodi, F. X., Retrolental fibroplasia, Am. J. Ophth. **34**:1, 1951.
10. Unsworth, A. C., Retrolental fibroplasia of premature infants, Tr. Am. Ophth. Soc. **47**:738, 1949.
11. Bosquet, F. P., Retrolental fibroplasia, in Second M & R Pediatric Research Conference, New York City, 1951, published by the M & R Laboratories, Columbus, Ohio, 1951, p. 29.
12. Owens, W. C., ibid., p. 59.
13. Guy, L. P., ibid., p. 32.
14. Levine, S. A., ibid., p. 35.
15. Powers, G., Some observations of feeding of premature infant, PEDIATRICS **1**:145, 1947.
16. Holm, E., Retrolental fibroplasia, Acta Ophth. **27**:623, 1949.
17. Magnusson, J. H., Retrolental fibroplasia, Ann. Pediat. **173**:246, 1949.
18. Soderhjelm, L., Personal communication to the authors.
19. Hess, J. H., Analysis of 259 living premature infants whose weight at birth ranged between 735 and 1260 gm., Chicago M. Soc. Bull. **51**:1057, 1949.
20. Gordon, H. H., Levine, S. Z., Wheatley, M. A., and Marples, E., Respiratory metabolism in infancy and childhood. XX. Nitrogen metabolism in premature infants: Comparative studies of human and cow's milk, Am. J. Dis. Child. **54**:1030, 1937.
21. Dean, R. F. A., and McCance, R. A., Inulin, diodone, creatinine and urea clearances in newborn infants, J. Physiol. **106**:431, 1947.
22. Young, W. F., Hallum, J. L., and McCance, R. A., Secretion of urine by premature infants, Arch. Dis. Childhood **16**:243, 1941.
23. West, J. R., Smith, H. W., and Chasis, H., Glomerular filtration rate, effective renal blood flow and maximal tubular excretory capacity in infancy, J. Pediat. **32**:10, 1948.

24. Rubin, M. I., Bruck, E., and Rapoport, M., Maturation of renal function in childhood, J. Clin. Investigation **28**:1144, 1949.
25. Gardner, L. I., and others, Etiologic factors in tetany of newly born infants, PEDIATRICS **5**:228, 1950.
26. Owens, W. C., and Owens, E. U., Retrolental fibroplasia: Studies in prophylaxis of disease; use of alpha tocopherol acetate, Am. J. Ophth. **32**:1631, 1949.
27. Josephs, H. W., Anemia of prematurity, Am. J. Dis. Child. **48**:1237, 1934.
28. Cooley, T. B., in Brennemann's Practice of Pediatrics, Hagerstown, Pa., W. F. Prior Company, vol. 3, chap. 16, p. 85.
29. LaMotte, W. F., Jr., and Tyner, G. S., Observations on retrolental fibroplasia, Arch. Ophth. **44**:620, 1950.
30. Klein, R., Adrenocortical control of sodium and potassium excretion in newborn period, J. Clin. Investigation **30**:318, 1951.
31. White, F. P., and Sutton, L. E., Jr., Observations on pituitary-adrenal response to epinephrine, PEDIATRICS **5**:876, 1950.
32. Gordon, H., Levine, S. Z., and McNamara, Helen, Feeding of premature infants, Am. J. Dis. Child. **73**:442, 1947.
33. Jeans, P. C., Feeding of healthy infants and children, J.A.M.A. **142**:806, 1950.
34. Mallek, M., and Spohn, R., Retrolental fibroplasia, Canad. M. A. J. **63**:586, 1950.
35. Woodbury, R. A., Robinow, M., and Hamilton, W. F., Blood pressure studies on infants, Am. J. Physiol. **122**:472, 1938.
36. Guyton, A. C., and others, Effects of massive transfusion and hemorrhage on blood pressure and fluid shafts, Am. J. Physiol. **163**:529, 1950.
37. Barnett, H. L., and others, Effect of ACTH on children with nephrotic syndrome. II. Physiologic observations on discrete kidney functions and plasma volume, J. Clin. Investigation **30**:227, 1951.
38. Hepner, W. R., Jr., Retrolental fibroplasia: Animal studies, to be published.

SPANISH ABSTRACT

Fibroplasia Retrolental: Observaciones Clinicas

Con el objeto de determinar si la alimentación con leche humana es capaz o nó de proteger al prematuro contra la fibroplasia retrolental, se realizóun experimento consistente en separar a 24 niños con peso entre 850 grms. y 1.540 grms., en 2 grupos iguales, alimentando a uno de ellos con leche humana que se había esterilizado al autoclave y al otro con leche de vaca semidescremada adicionada con 10% de hidratos de carbono y esterilizada también al autoclave. El grupo de niños alimentado con leche humana la recibió hasta alcanzar un peso de 1.800 grms. No hubo diferencia alguna, ya que en ambos grupos 3 niños presentaron fibroplasia retrolental. Aunque es pequeño el número de pacientes estudiados, parece razonable concluir que la alimentación exclusiva con leche humana, a prematuros pequeños y hasta que estos tengan un peso de 1.800 grms., no prevee el desarrollo de la fibroplasia retrolental.

Un posible factor es la retención de líquidos, observable en los niños alimentados con leche humana cuando se les cambia a leche de vaca, especialmente si a esta se le ha agregado carbohidratos que contengan cloruro de sodio.

Para descubrir si las transfusiones sanguíneas podían tener algún efecto en la fibroplasia retrolental, se revisaron las historias clínicas de 20 niños con peso al nacimiento menor de 1.500 grms. Ocho tuvieron fibroplasia retrolental y 12 no la presentaron. Aunque ambos grupos tenían una alimentación con el mismo número de calorías por kilogramo de peso corporal, los niños con fibroplasia retrolental aumentaron de peso mas rápidamente. Todos los de dicho grupo habían recibido transfusiones observándose que el volumen de ellas, por kilogramo, era también mayor que el que se había utilizado en las transfusiones de los prematuros que no enfermaron. Después de haber recogido esos datos se estudiaron las historias clínicas de 22 enfermos con fibroplasia retrolental. Todos menos 2 habían recibido transfusiones antes de que hubiera evidencia alguna de dicha enfermedad. Los estudios de control no fueron factibles.

Es posible que en niños con desprendimiento temprano de la retina por fibroplasia retrolental, el ACTH actúe en el metabolismo del agua, así como en la actividad fibroplástica y de tejido neo-

vascular. El efecto primario podría ser la producción de diuresis de agua y sodio y la redistribución de los electrolitos y del agua retenidos.

La alimentación a base de fórmulas con concentración electrolítica alta y las transfusiones sanguíneas voluminosas son capaces de rebasar en el niño prematuro pequeño, las capacidades fisiológicas de control, conduciendo a la fibroplasia retrolental. Se presentan los casos de 2 niños en los que pareció existir una relación directa entre el desarrollo de ella y las transfusiones sanguíneas verificadas durante un período de retención hídrica y de electrolitos. El procedimiento de alimentar al niño prematuro con una fórmula de alta concentración electrolítica, y el de administrar transfusiones sanguíneas excesivas, pueden ser responsables de las variaciones notables observadas en la incidencia de esta enfermedad entre un hospital y otro y aún en una misma institución, y del aumento en frecuencia de la fibroplasia retrolental observado después de la introducción de estros métodos.

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SOME EMOTIONAL PROBLEMS ASSOCIATED WITH RESPIRATORY INSUFFICIENCY IN POLIOMYELITIS

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EVERY physician who has cared for a patient acutely ill with poliomyelitis is necessarily impressed with the psychologic impact of this disease. Yet if a search is made for writings on this subject, little information is found.[1-4] There may be several reasons for this. Poliomyelitis as an acute disease is of relatively short duration, and in a general sense the issue is promptly determined. As a consequence, the physician has little opportunity to collaborate with the psychiatrist, or to evaluate the emotional status of his patients with a view toward clinical investigation of the point. Probably of greater importance is the physician's knowledge that psychologic problems differ only in degree from those associated with other diseases. Stated another way, he is on familiar, though very difficult and perplexing ground.

Since poliomyelitis is an epidemic disease, it frequently follows that the work-load of the physician does not permit allocation of time necessary for proper handling of emotional problems. This becomes particularly true if the diagnosis automatically means admission to a "Polio Unit." Facilities in such units are primarily geared to specialized care of a few complicated and severe cases, but may become overcrowded and understaffed by the unselective and routine admission of any affected individual. Only the "don'ts" of dealing with social and psychologic problems can be recorded from such experiences.

In this discussion, interest is chiefly in the respiratory complications of poliomyelitis, but from the standpoint of the patient's emotional reactions we cannot disregard a compounding of anxiety-producing factors. First, we are dealing with a sick individual and the constellation of his family and community. Secondly, we are concerned with a particularly dreaded disease; one which seems to strike at random, and, in the minds of the laity, results in permanent crippling. Finally, compromise of respiratory function, from whatever cause, is a terrifying experience to any conscious individual. An effective therapeutic effort designed to promote psychologic well-being must consider all such parts of the problem.

A proper beginning is made when the physician first sees a suspected case. The patient and/or his family deserve orientation with respect to what lies ahead. They should be made to realize that many patients recover essentially normal function even if true paralysis is present. They should be advised of the facilities available in their community to meet various contingencies. Particularly in the case of parents, the exposure of other members of the family should be discussed. Advice should be offered as to what restrictions of family activities are warranted, and for how long. Counsel can be given on how best to meet difficult social situations which occasionally result from community hysteria. All pos-

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sible help must be given to insure against financial hardship to the breadwinner of a family. A call from the doctor to the patient's or the parent's employer is often useful in this connection, or the efforts of a social worker are frequently helpful. The individual can be assured that inadequate funds will not deprive him of needed care. The alternatives of home care versus hospitalization should be explained. The patient and his family will be better able to accept hospitalization if they have been forewarned and understand the indications for it. On the contrary home care will be more satisfying if there is realization that facilities of the "Polio Unit" are limited and must be reserved for patients needing special care. Finally, in most instances, it is advisable to tell the patient or a responsible member of his family what can be reasonably expected in a particular case. Such expressions obviously must be tempered by good judgment, and should have as their aim the establishment of confidence and trust in the physician.

In the event hospitalization is required it is important that the reasons for prohibition or restriction of visiting are well understood. When transfer of professional responsibility to other than the private physician is necessary, a great deal of uneasiness can be avoided if the advantages of several physicians combining their special skills as a team are pointed out. Short visits from the private physician, when possible, also help the patient accept somewhat less personalized care. By the same token, every effort must be made by the hospital staff to foster patient morale. It is the physician's responsibility, whether in the home or on a special hospital service, to explain what is going on, to anticipate the anxiety of patient and family, and even to accept and interpret resentment as a manifestation of insecurity. Only under exceptional circumstances can the physician delegate this duty. It is not implied, however, that support in his efforts by social workers, nurses and others is undesirable; on the contrary, if integrated with the over-all plan of management such services are truly invaluable. At times the work of available medical personnel must be reduced to a minimum, in which case it is far better to delegate responsibility for patient and family relationships to an intelligent and interested social worker or nurse than to grossly underestimate their importance by ignoring them. Throughout hospitalization the importance of repeated interviews as a vehicle for examining each new problem as it arises can hardly be over-emphasized. Hoekstra[1] has stressed the advantages of psychiatric orientation during interviews in helping the patient and others to release emotional tension.

In the care of individual patients certain principles can be defined. Their pursuit assumes special importance in the presence of bulbar, bulbo-spinal or cervical involvement. The utter dependence of such patients upon those caring for them is pathetically apparent. Absurdly trivial incidents take on exaggerated significance, and the patient too easily reflects or magnifies the emotional tone of his immediate environment.

The patient in a respirator must be surrounded by friendliness, without excessive solicitude, by quiet efficiency, and by the confidence among personnel which comes from knowledge of their proficiency. Necessary procedures must be undertaken with despatch and without hesitation, and the patient advised as to what is expected. Insofar as possible routines should be adapted to emotional needs and individual preferences. A wise physician is on the alert for personality clashes particularly involving nurses and patients. Not infrequently, shifts of personnel may be the only means of resolving these difficulties. A most graphic example came to my attention soon after an experienced and efficient nurse, who preferred caring for male patients, was transferred to a small ward of female respirator cases. Patient morale suffered immediately. One patient who had been able to

stay out of the respirator for considerable periods seemed to have lost all interest in the struggle. She became apprehensive and unusually quiet. Within 2 or 3 days complaints were heard, though not substantiated, to the effect that if the nurse became displeased, bedpans were not brought promptly, hair combing was accomplished with unnecessary roughness, or painful extremities were not respected in accomplishing necessary care. Whether real or imaginary, the situation was adversely affecting patient recovery, and was promptly corrected by the assignment of a much less proficient but fortunately compatible nurse to these patients.

In caring for a person with poliomyelitis through the cooperative efforts of several physicians, it is highly desirable that one member of the group, preferably a pediatrician or internist, assume responsibility for over-all direction. By this device, the integrity of the patient as a total functioning person is best maintained and his professional dissection into skeletal system, nervous system, respiratory system, and so forth is prevented. An illustrative example of professional preoccupation with a single facet of the clinical problem was offered by the case of an adolescent boy who had been painstakingly prepared for removal from a respirator. His progress had been entirely satisfactory until the occasion of a nonessential and perhaps poorly executed examination of muscle strength. The patient did not have to be a genius to realize the meaning of, "quadriceps femoris, one on the right and two on the left," and a second later, "Well, look here, toe flexors four plus." He had undoubtedly realized quite clearly before that time that the involvement of his lower extremities was rather extensive, and had probably assiduously avoided facing that problem while meeting more immediate ones. Faced with this apparently inescapable evidence of handicap, he seemed to be overcome by feelings of hopelessness and the futility of trying. The obvious result, which might have been anticipated and prevented, was a considerable further delay in attaining independence from artificial respiration.

Among the more complex problems faced by physicians is deciding how accurately and completely the patient's questions should be answered. Curiosity on the part of the sick individual is usually extreme, but a full and candid report may be unnecessarily brutal. Too restricted an answer, or evasion, on the other hand, may seriously imperil the patient's confidence in the physician. The manner in which this dilemma is resolved will depend not only upon the personality and experience of the physician, but also upon knowledge of his patient. Undoubtedly situations exist in which some deception of the individual may be, at least temporarily, justifiable and necessary. Far more often it is a mistake which in the long run is more traumatic than the truth would have been. One child I remember would have nothing to do with a well-meaning physician who, at the time of respirator placement, described the apparatus as a test which was to be run for a little while. Subsequently this physician's approach invariably evoked a reaction of stubborn defiance. Deception of another sort is exemplified by attempting to decrease the pressure in a respirator without the knowledge of the patient. This maneuver similarly can backfire as it did in the case of an adolescent girl who had insomnia for several days after discovering the ruse. Considerable effort and valuable time were expended in regaining her confidence. Finally, in this connection the error is sometimes made of being overoptimistic in the hope of offering increased incentive to a patient. When it becomes apparent that the desired goal cannot be reached, the patient is abruptly "let down" and may react with serious depression. A physician with primarily cervical cord involvement who was under my care reacted in this manner to over-zealous efforts toward removing him from the respirator. He had been built up for a let-down and in consequence became

not only depressed, but also excessively anxious at any adjustment of the respirator controls.

At this point it is pertinent to consider dangerous misinterpretations of patient behavior. At times there is real temptation to explain the complaints of the respiratory cripple on the basis of neuroticism. The potential fallacy of this presumption is apparent in the individual who is receiving adequate oxygen, but has hypercapnia by reason of inadequate or ineffective pulmonary ventilation. Further, as Elam has shown,[5] there are instances in which patients become acclimated to hyperventilation and experience real discomfort when the respirator is adjusted to furnish more normal ventilatory volumes. Since most of us are not able to employ an elaborate combination of diagnostic tools such as the pneumotachograph, oximeter and carbon dioxide analyzer in the accurate appraisal of respiration, we must be especially alert to the possibility of such findings and subjective symptoms as restlessness, increasing anxiety, irritability, and flushing being due to altered respiratory physiology. Also in this connection we must be increasingly circumspect in applying the phrase "habituation to the respirator."

Increased understanding of poliomyelitis has made relaxation of many quarantine and isolation precautions possible and has removed it from the "pest house" category of disease. As a consequence, visiting is usually allowed after the first week. In addition the immediate family are usually allowed supervised contact with critically ill patients even during isolation. Since most respirator patients are considered critically ill, at least during the acute stage of the disease, the regulation and orientation of visitors becomes a matter of considerable importance. Excluding those few persons who unfavorably influence the patient by failing to control their own emotional tensions, most visitors have a salutory effect, and should be encouraged. For young children the presence of a parent adds greatly to feelings of security and often allows for the accomplishment of necessary procedures with a minimum of emotional disturbance. To older children and adults visitors may seem less vital, but they nevertheless remain as a primary consideration for the maintenance of morale. While it is often wise to allow long visiting periods for the parents of a young child especially during the first days of illness, visits to older patients are better restricted to short periods, frequently repeated. The latter group feel the need of exerting themselves in the presence of their guests; perhaps attempting to reassure a family member; perhaps offering solutions to home problems which have arisen in association with the illness; or perhaps trying to ferret out information which he believes is being withheld. In contrast, we have probably all seen the small child who interrupts needed rest only long enough to assure himself that his mother or father is nearby.

The complexity of interpersonal relationships being extreme, general recommendations must always be modified to meet individual circumstances. Thus a highly emotional, oversolicitous parent or relative may upset the patient to such an extent that restriction of visiting is necessary, and certainly to the point that prolonged visits should be tactfully discouraged. Similarly abnormal life situations involving adults call for drastic modification of the usual attitude toward visiting. Recently, on our poliomyelitis service, a young married woman was admitted with severe and rapidly progressive bulbo-spinal involvement. It was considered strange that the husband had not been in to see his wife by the second day, but soon thereafter he walked in, apparently unconcerned, accompanied by another woman in whom he was obviously interested. The patient in question seemed to sense the seriousness of her condition from the repeated consultations held concerning her; was aphonic as a consequence of tracheotomy performed before she was placed in a respirator; and as was learned later, was terrified by the prospect of a faithless and

brutal husband together with an equally disinterested and loathsome woman caring for her only child then 6 years of age. This unfortunate individual could not even appeal for help. Obviously such unfortunate occurrences cannot always be prevented, but they do serve to emphasize the necessity of continued alertness for psychologic factors which might adversely affect the patient.

Liberal interpretation of visiting regulations and openmindedness can, on occasion, lead to most gratifying results. Such expedients as moving the respirator of an eight year old boy to a window from which he could see his dog involved some trouble, but was rewarding and important therapy for the patient. By the same token an arranged visit from the employer of an ambitious young business man allayed his fears about losing a cherished job, and as would be expected, greatly improved his emotional outlook. It is my firm conviction that this patient's subsequent, rapid improvement was attributable in considerable part to the removal of an important source of emotional turmoil, thereby allowing him to concentrate fully on the immediate problem of his recovery.

Before leaving the discussion of visitors, occasional difficulties in connection with religious principles and practices deserve mention. These can be roughly divided into two types. The first arises when the hospital staff is not sufficiently sensitive to the religious needs of its patients. The services of minister or priest are often of unquestionably great comfort. In addition, an experienced and wise clergyman is exceptionally well prepared to help with the solution of emotional problems, and usually can be helpful in social problems as well. If given opportunity he is more than willing to integrate his efforts into the total plan of management, and can be of invaluable assistance. Infrequently conflicts arise as to the priority of ministrations by doctor and churchman. The author can only express his personal conviction, without presuming that it will satisfy others. In my opinion, as long as there is a living patient for whom any medical examination or procedure offers some hope, the physician must be given the opportunity of carrying these out without interference by religious ceremonies or functions. Further, the physician should be in a position to point out frankly the fact of a particular patient reacting unfortunately to the approach or personality of a particular church representative, and at the same time to suggest a change of religious advisors. Such recommendations are in no sense an insinuation of censure or criticism, but rather, are made in an effort to help the patient and to point out the reality of personality conflicts as they may occur between any two individuals.

Returning to more objective aspects in the management of respirator patients with poliomyelitis, careful thought should go into the planning of daily routine activities. Adequate consideration must be given, of course, to the accomplishment of necessary therapeutic procedures, but in addition, care must be exercised to avoid excessive fatigue; to prevent long periods of inactivity which are conducive to dangerous introspection; to encourage companionship with other patients; to insure the inclusion of adequate diversion; and last but most important to impose certain responsibilities upon the patient. He should be made to feel that although he will receive all possible technical and professional assistance, optimal recovery will depend on his own efforts. An attitude of passive nonparticipation characterized by the patient who says in effect, "Here I am, now it is your job to cure me," is neither healthy for the individual nor conducive to the best therapeutic result. Conformity to a schedule of appointments during each day is an important tool for combatting such mental attitudes in an immobilized individual.

Respirator patients, whenever possible, should be grouped together. Man, a gregarious creature, measures his attainments in comparison to those of others. Granted that his competitive urges do not always lead to peace of mind, nevertheless they are an integral

part of his way of life, and should not be ignored. Further, every individual possesses pride, and in the presence of his fellows likes to make a good showing. The family of a private patient usually will insist on a private room, but after a few days the patient himself will begin to realize the disadvantages of his isolated position. From the remarks of doctors and nurses concerning the progress of other patients, his curiosity will be aroused. Consciously or subconsciously he will want the companionship of persons who face similar problems. His adjustment into such a society is an important early step in rehabilitation. Excessive self-pity will not be tolerated by his fellows; he will begin to inventory what functional abilities he possesses in comparison to others, rather than being preoccupied with what has been lost temporarily or permanently; he will realize the progress made by patients whose illness antedates his own; and importantly he will have to exercise his sense of humor again. In aggregate these efforts mean effective participation in a therapeutic program.

In the preceding discussion some of the general therapeutic approaches to the solution of psychologic and social problems among patients with respiratory difficulties have been reviewed. When we recall that at present there is still no specific therapy in poliomyeliits, and that our efforts are almost exclusively supportive, emphasis on the emotional well-being of our patients has obviously great importance. Without deprecating the essentials of objective, quantitative measurement in managing respiratory impairment, the fact remains that important factors in patient response are not so measurable. These latter are determined by the emotional patterns and life situations of the individuals concerned. Whether we describe the skillful handling of these as the art of medicine, practical psychiatry, or just plain common sense makes little difference. The important considerations are to anticipate these emotional difficulties and then to evaluate our therapeutic regimes critically in relation to the particular conflicts encountered in each patient under our care.

References

1. Hoekstra, C. S., Psychiatric reaction to acute anterior poliomyelitis, Rocky Mountain Conference Infantile Paralysis, 1946, pp. 69-74.
2. Crothers, B., and Myer, E., Psychologic and psychiatric implication of poliomyelitis, J. Pediat. **28**:324, 1946.
3. Seidenfeld, M. A., Psychological aspects of poliomyelitis, PEDIATRICS **4**:309, 1949.
4. Poliomyelitis, Papers and discussion presented at the First International Poliomyelitis Congress, Philadelphia, J. B. Lippincott Company, 1949.
5. Grulee, C. G., Jr., and Elam, J. O., in Round Table Discussion on poliomyelitis, PEDIATRICS **1**:684, 1948.

Spanish Abstract

Algunos Problemas Emocionales Asociados con la Insuficiencia Respiratoria de la Poliomielitis

El autor hace una revisión de las medidas terapéuticas generales para lograr la solución de los problemas psicológicos y sociales de los enfermos poliomielíticos con trastornos respiratorios, haciendo énfasis en que el bienestar emocional de estos pacientes es de gran importancia dado que hasta el momento actual no existe una terapéutica específica de la poliomielitis y ésta se reduce en realidad a terapia de sostenimiento.

Existen factores importantes en cada individuo que son determinados por sus patrones emocionales y circunstancias de la vida que son decisivas en la respuesta del enfermo y que no son mesurables. Que el manejo habil de estos factores sea catalogado como arte de la medicina, psiquiatría práctica o simplemente sentido común, no importa, la consideración importante es anticipar estas dificultades emocionales y entonces evaluar criticamente nuestros regímenes terapéuticos en relación con el conflicto particular encontrado en cada paciente.

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STUDIES OF THE IMMUNOLOGY OF THE NEWBORN INFANT

III. Permeability of the Placenta to Maternal Antibody During Fetal Life

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THE premature infant is generally considered more susceptible to infection than older infants. In reviewing the possible reasons for this, it is important to know whether, in being born before term, he has received his normal share of maternal antibody, and whether if he has received it, he retains it as long as a term child.

The human placenta near term is permeable to many antibodies including diphtheria antitoxin, and at term the maternal level and the infant level of these antibodies are approximately equal.[1-4] However, it is not known how early in fetal life this free permeability develops.

More than half of the adults in the New York area carry circulating diphtheria antitoxin, derived from previous immunization or experience with the infection. Taking advantage of this, the authors have been able to study the maternal and cord bloods of 56 premature infants from the Premature Service of Bellevue Hospital who were found on routine examination to have circulating diphtheria antitoxin. By comparing the maternal and infant antitoxin levels in each pair of bloods, they have a measure of per cent transmission of antitoxin through the placenta, which can be compared with length of gestation as indicated by birth weight.

In addition, in order to determine whether a premature infant retains maternal antibody as long as a term infant, a small group of premature infants who had received diphtheria antitoxin by passive transfer from the mother was followed over a period of months. The antitoxin level of the blood was investigated at intervals and the rate of fall determined.

A. PLACENTAL TRANSFER

MATERIALS AND METHODS

Diphtheria antitoxin was selected as the antibody for study because (1) its measurement is relatively simple and quantitatively accurate and (2) a large number of mothers will normally have rather high levels of diphtheria antitoxin in their blood.

Arrangements were made to have a sample of maternal and of cord blood collected at each delivery of a premature infant at Bellevue Hospital. Serum diphtheria antitoxin was measured as soon as possible after collection by the rabbit Schick test technic[5] and pairs of blood samples in which the maternal level was over .002 units/cc. were saved for careful titration. In some infants,

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TABLE 1

DIPHTHERIA ANTITOXIN CONTENT OF MOTHER'S BLOOD AND INFANT'S CORD BLOOD IN UNITS/CC. SERUM, OF 56 INFANTS. GESTATION PERIOD IS CALCULATED FROM LAST MENSTRUAL PERIOD

Birth Wt. (gm.)	Wk. of Gestation (Calc. From L.M.P.)	Mother's Diphtheria Antitoxin u./cc. serum	Cord-Blood Diphtheria Antitoxin u./cc. serum
50	20	.04	.008
430	—	3.75	.75
430	—	3.75	1.0
500	26	.1	.01
640	27	.2	.1
820	25	.2	.05
850	27	.03	.02
860	—	.25	.1
930	31	.1	.04
940	21	.5	.2
950	—	1.0	0.5
950	31	.15	.10
980	33	1.0	.75
990	25	.15	.15
1020	—	.25	.15
1050	28	.5	.15
1050	30	.15	.05
1070	37	.5	.2
1150	—	.5	.5
1200	21	.006	.03
1200	27	.1	.03
1280	44	.15	.15
1280	38	.5	.2
1380	30	.2	.1
1390	35	.5	.75
1418	33	1.0	.5
1450	—	0.05	.05
1490	35	.75	.5
1510	31	.75	.5
1550	30	.03	.02
1560	—	.25	.15
1590	31	.1	.1
1600	34	.5	.5
1640	30	.03	.02
1690	—	.2	.1
1750	21	.15	.1
1760	28	.1	.1
1780	—	.5	.5
1790	37	.03	.02
1810	—	.03	.02
1830	32	5.0	0.5
1870	34	.2	.2
1930	36	.15	.1
2000	40	.01	.03
2000	34	.02	.01
2000	34	.02	.02
2010	35	.75	1.0
2040	38	.75	.75

TABLE 1 (*Continued*)

Birth Wt. (gm.)	Wk. of Gestation (Calc. From L.M.P.)	Mother's Diphtheria Antitoxin u./cc. serum	Cord-Blood Diptheria Antitoxin u./cc. serum
2050	37	.03	.04
2120	34	.1	.1
2130	35	.75	1.0
2160	39	.75	.5
2240	—	.75	.75
2270	43	.004	.004
2310	36	.04	.01
2600	39	.1	.05

additional blood samples were obtained at weekly and then monthly intervals to measure the rate of fall of antitoxin level.

For purposes of this study, cord blood is taken to represent infant's blood at birth.[3] Although this is not strictly true, the error is very slight compared to the larger differences found between cord and maternal blood.

Results

Table 1 represents the maternal and infant-cord serum antitoxin levels for 56 infants, in order of birth weight. The smallest fetus obtained weighed about 50 gm. and the largest infants approached normal birth weight. As a second measure of maturity of the infant the gestational age was calculated from the last menstrual period, when known.

There is considerable variation in the antitoxin titer of the maternal bloods, and also in the relation of cord blood titer to maternal titer, yet there is a persistent tendency for the cord blood titer to be less than the maternal in small infants, and about equal to the maternal titer in large infants.

Chart 1 represents an attempt to interpret this data statistically. Because the method of measurement requires progressive logarithmic steps in unitage measure, it is appropriate to express the diphtheria antitoxin concentrations on a logarithmic scale. For the same reason, more information can be obtained if the logarithms of the concentrations of antitoxin of mother and child are compared than if the arithmetical values are compared directly.

Chart 1 presents graphically the difference between the logarithms (to the base 10) of the serum antitoxin concentrations of maternal and cord specimens, for all infants studied, in relation to birth weight. If the infant (cord) titer is much less than the maternal titer, the difference will be positive and large, so the pair will appear as a dot high on the graph. If the titers of mother and child are exactly the same, the dot will appear on the horizontal mid-line. If the infant titer is higher than the maternal titer, the dot will fall below the midline.

It is apparent by inspection of chart 1 that the small infants (presumably of short gestation) tend to have clearly less antitoxin than their mothers, while the large infants (presumably of near normal gestation) tend to have close to the same concentration of antitoxin as the mother.

The regression line for this data has been calculated from the equation $Y = 0.199 - 0.00318\ (X\text{-}1452)$ where Y equals estimated difference: ($\log_{10}$ maternal titer $-$ $\log_{10}$ infant cord titer) and X equals birthweight in grams.

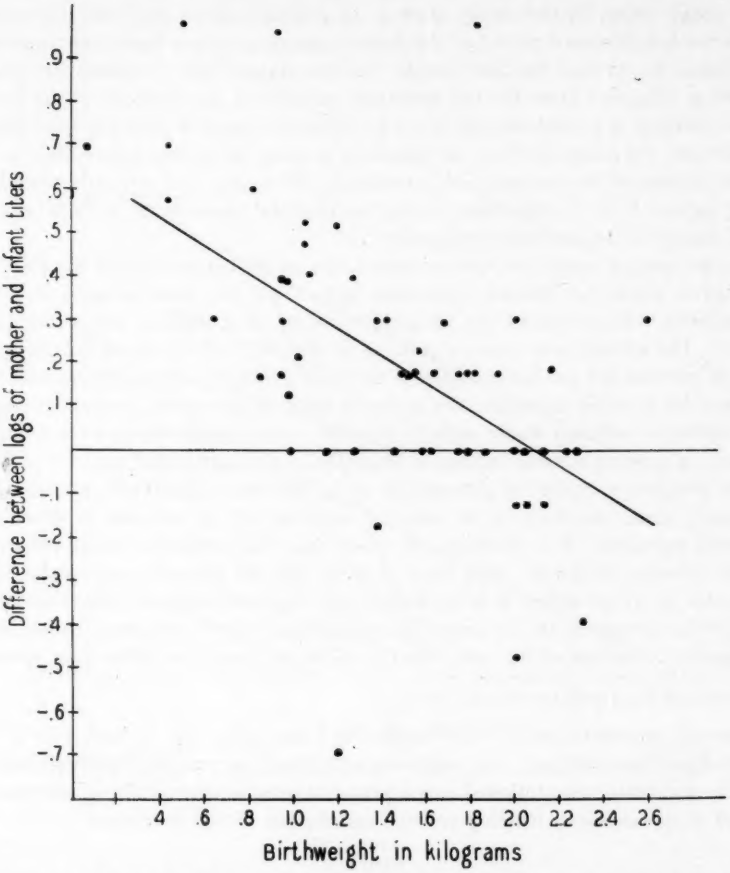

CHART 1. Relation of birthweight of premature infants to placental transfer of diphtheria antitoxin. Placental transfer is represented as difference between $\log_{10}$ of antitoxin concentration of maternal and of cord blood.

As a test of the validity of the regression line, the correlation coefficient was found to be −.530, significant at the 1% level, showing that the slope of the regression line can be regarded as real.

DISCUSSION

It is not possible from this data to determine exactly when the placenta becomes freely permeable to diphtheria antitoxin. Using a rather arbitrary line of division, infants under 1200 gm. appear to be deficient in maternal antibody; while infants above that weight appear, as a rule, not badly deprived. The regression in chart 1 suggests that there is a progressive increase in placental permeability as the birth weight increases.

It is difficult to translate this information into terms of gestational periods. The birth weight is widely used as a measure of the duration of pregnancy, but at best it can only

be a rough index. Unfortunately, there is no accurate measure available at present. At times the last menstrual period of the mother appears to give a better indication of the gestational period than the birth weight. For this reason, table 1 includes the gestation period as calculated from the last menstrual period as it was recorded in the mother's chart. However it is doubtful that it can be regularly depended upon any more than the birthweight and it does not have the advantage of being objectively determinable as is the latter. In view of the inaccuracy of our measure, the authors can only state roughly that there appears to be a progressive increase in placental permeability to diphtheria antitoxin during the last trimester of pregnancy.

Flexner and his associates[6] have presented data on the permeability of the placenta to radioactive sodium at different gestational ages. Their data show a linear increase in permeability with gestational age, of qualitatively the same general form as this data in chart 1. The authors have drawn a curve to fit their data which would indicate a sharp drop in permeability just before delivery, but there is not presented sufficient data to tell whether this is merely a deviation due to chance alone. In general the present authors' data for diphtheria antitoxin would seem to resemble rather closely the data for radioactive sodium, in showing a linear increase in transmission with gestational age.

The progressive increase in permeability of the placenta to diphtheria antitoxin during pregnancy seems therefore to be merely a reflection of its increased permeability to diffusible substances. It is reasonable to expect that other antibodies would behave in a similar fashion, though we must keep in mind that the placenta may not be equally permeable to all antibodies. It is not known how important transplacental maternal antibody is to a newborn infant but it must be assumed that it may be important. Its low level in prematurity is another of the many hazards which the premature infant must surmount.

B. Rate of Fall of Antitoxin Titer

Fourteen premature infants who weighed less than 2000 gm. at birth (six of these weighed less than 1600 gm.) and who had titers of over .01 units/cc. diphtheria antitoxin in their cord blood were followed over a period of months. The circulating antitoxin was titrated at approximately monthly intervals and the rate of fall determined.

TABLE 2

Rate of Fall of Transplacentally-Received Diphtheria Antitoxin in 14 Premature Infants

Birth Wt. (gm.)	Cord Blood	1–2 wk. of age	1–2 mo. of age	3–4 mo. of age	5–6 mo. of age
1050	.15	.15	.1	.03	< .002
2000	.01	.02	.004	< .002	
2040	.75	.5 (approx.)	.5	< .002	
1280	.15	.15	.1	.01	
1560	.15	.15	.15	.01	
950	.1	.05	.05	.02	
1930	.1	.1	.1		
1600	.5	.5 (approx.)	.5	< .002	
2310	.1		.02		
1680	.04	.04	.02	.008	
1640	.02		.006	.002	
1780	.5		.2; .1	.02	
1760	.1		.04; .02	< .002	
1150	.5		.05	.02	

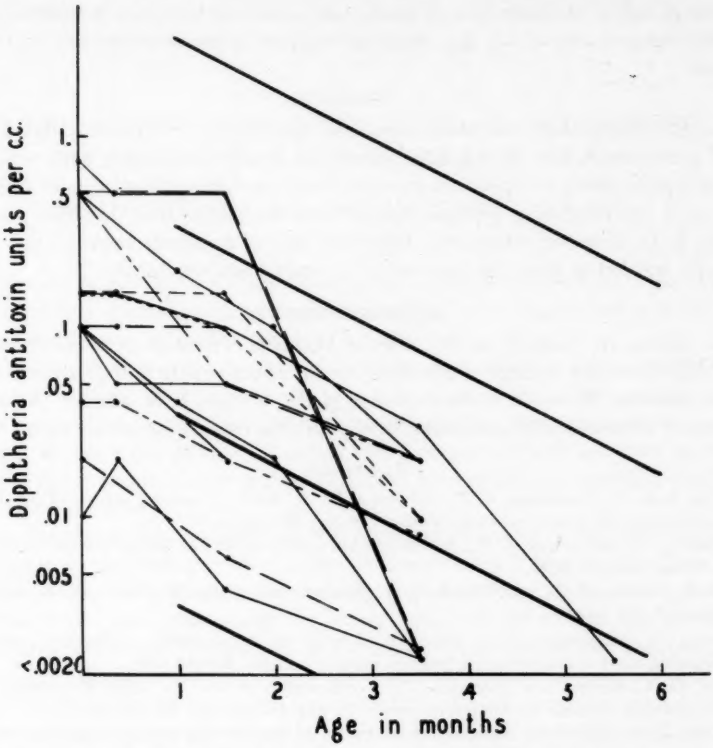

CHART 2. Rate of fall in transplacentally-received diphtheria antitoxin in 14 premature infants as compared to full term infants.

RESULTS

The results are presented in table 2 and in chart 2. In chart 2 the heavy lines represent the rate of fall of transplacentally received antitoxin in full term newborn infants as calculated from the formula of Barr and Glenny[3] which was derived from a study of 50 normal newborn infants.

DISCUSSION

The data are insufficient for statistical analysis; however, simple inspection of chart 2 indicates that there is no great difference between newborn infants and premature infants in the rate of fall of antitoxin titer. The antitoxin titer in a particular infant at a particular time depends largely on the concentration of antitoxin at birth and the infant's age in prematures just as in normal infants. This is what would be expected if the antitoxin were handled in the same way as any passively-received homologous protein. The concentration should gradually fall as the protein is metabolized or is diluted by the increasing volume of body fluids that takes place with growth. While there are known to be some differences between prematures and full term newborns in the rate of growth and in the utilization of protein, these differences are not so great as to lead one to expect an obvious change in

the rate of fall of antitoxin titer. It would take a much larger series to demonstrate the slightly increased rate of fall that would be expected in premature infants, on theoretic grounds.

Summary

The titer of diphtheria antitoxin in maternal and infant (cord) blood was compared in 56 premature infants. A significant correlation was found between birth weight and placental permeability to diphtheria antitoxin. Small premature infants (under 1200 gm.) have much less circulating antitoxin derived from the mother than do larger premature infants. In 10 premature infants with high cord titers of diphtheria antitoxin, this passive immunity was lost at about the same rate as by normal newborn infants.

Acknowledgment

The authors are indebted to Dr. Donald Mainland, Professor of Medical Statistics, New York University College of Medicine, for his extensive help in the statistical evaluation of this data. Gratitude is also expressed to Dr. William E. Studdeford, Jr., and the residents of Obstetrics and Gynecology Service for their cooperation in this study.

References

1. Lichty, J. A., Jr., Katsampes, C. P., and Baum, W. S., Study of humoral antibodies for staphylococcus aureus in infants and their mothers, J. Pediat. **22**:549, 1943.
2. Gordon, J. E., and Janney, J. H., Antistreptolysin content of sera of normal infants and children, J. Pediat. **18**:587, 1941.
3. Barr, M., Glenny, A. T., and Randall, K. J., Concentration of diphtheria antitoxin in cord blood, Lancet **2**:324, 1949.
4. Liebling, J., and Schmitz, H. E., Protection of infant against diphtheria during first year of life following active immunization of pregnant mother, J. Pediat. **23**:430, 1943.
5. Fraser, D. T., presented by Fitzgerald, J. G., Technique of method for quantitative determination of diphtheria antitoxin by skin test in rabbits, Tr. Roy. Soc. Canada. **25**:175, 1931.
6. Flexner, L. B., and others, Permeability of human placenta to sodium in normal and abnormal pregnancies and supply of sodium to human fetus as determined with radioactive sodium, Am. J. Obst. & Gynec. **55**:469, 1948.

Spanish Abstract

Estudios de Inmunología en el Recién Nacido III. Permeabilidad de la Placenta a los Anticuerpos Maternos Durante la Vida Fetal

Se investigó en 56 niños prematuros la permeabilidad de la placenta a la antitoxina diftérica materna en diferentes edades del embarazo, usando solo a aquellas madres que tenían antitoxina diftérica circulante en el momento del parto y comparando sus titulos de antitoxina con los de sangre del cordón del niño. En esta comparación se vió que los niños prematuros grandes, de más de 2 Kgs, tenían aproximadamente la misma cantidad de antitoxina diftérica circulante que sus madres; contrariamente, en los prematuros pequeños, de menos de 1.200 Kgs. al nacer, que se les presume de menor edad de embarazo, sus títulos de antitoxina eran notablemente mas bajos que los de sus madres.

De lo anterior se concluye que la permeabilidad de la placenta a las antitoxinas maternas aumenta durante los últimos tres meses del embarazo.

En 10 prematuros que tenían títulos altos de antitoxina diftérica en la sangre del cordón y en los que se hicieron titulaciones seriadas durante varios meses después del nacimiento para estudiar su descenso y desaparición se encontró que perdían su inmunidad pasiva con la misma rapidez que los niños normales nacidos a término.

477 First Avenue

THREE YEARS' EXPERIENCE WITH AN AFFILIATED RURAL RESIDENT TRAINING PROGRAM

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FOR several years medical educators have given increasing consideration to the problem of extending medical teaching beyond the period of medical school and residency training, into the area of medical practice.

Dr. Edwards A. Park[1] forcibly outlined this concept when he wrote, "Perhaps the greatest benefit which could be brought to pass in medical care in this country would result if the medical schools could be made to descend from their ivory towers—to use Dr. James Wilson's metaphor—and extend their educational facilities to the practicing physicians of the country and to assume the task of keeping them informed as a full part of their responsibilities."

A few months later a committee of the American Academy of Pediatrics reported,[2] "In its report to the Executive Board at the Academy's Annual Meeting in Atlantic City, November 20-23, 1948, the Committee on the Improvement of Child Health gave due recognition to the great progress over the last half century in the medical care of children, but emphasized that the full benefits of modern medical care are not available to all children. The Committee's overall recommendations based on the findings are twofold:

"(1) To strengthen pediatric training in medical training in medical schools so that all doctors, not only specialists, may be thoroughly prepared to care for children, and

"(2) To develop systems of decentralized training and rural extension services so that better medical care for children may be available in outlying areas."

In view of the widespread interest in this concept and also in methods of developing a workable system of extending the services of a modern teaching center, it is felt that a description of the Children's Hospital-Imperial County Project might be of interest.

During the early spring of 1948, conversations between representatives of the State of California Department of Public Health and the late Dr. John D. Lyttle, then Director of the Children's Hospital, Los Angeles, and Professor of Pediatrics, University of Southern California Medical School, regarding field experience for residents of the Children's Hospital, indicated that the medical school and hospital would be deeply interested in such a project.

The next step was to find a rural area in which medical and community interest could be stimulated. Exploratory discussions in Imperial County with the County Medical Society, the Health Officer and the Board of Supervisors indicated that this area was interested and willing to undertake a cooperative program of this type.

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The Plan

The detailed plan was carefully evolved by Dr. Lyttle, the Imperial County Medical Society, the Health Officer, and the Board of Supervisors of Imperial County and became effective on October 1, 1948.

It was agreed that each year four senior residents in pediatrics at the Children's Hospital would spend two months each, working in the Imperial County Hospital. In order to maintain some continuity in the service, a few days of overlapping was planned at the end and the beginning of each period of service.

The residents were to work under the supervision of the Medical Director of the County Hospital and the local hospital visiting staff. They would assume resident responsibility for the pediatric patients in the hospital, the newborn service, the pediatric outpatient service, and in addition would assist in the hospital prenatal clinics and obstetric service. It was estimated that the hospital service would require about half the residents' time, the remainder would be spent in services for infants and children conducted by the County Health Department. This public health activity would consist of conducting well child conferences, selected school health services, assisting in crippled children's clinics, and some work with community groups in medical educational projects.

In order to strengthen this extended service by direct consultation and supervision, the Department of Pediatrics, U.S.C., agreed to conduct monthly two day clinical conferences in the Imperial County Hospital. This service, provided by the most experienced members of the senior attending staff of the Children's Hospital, would be available not only to the resident but would also include all the local physicians.

The visiting staff spent a part of this two day visit making rounds in the County Hospital with the resident, concentrating on the difficult diagnostic and treatment problems. The local physicians were invited to attend these informal rounds and to present any of their individual problems for consultation.

Each year, at the time of the first clinical conference, the local physicians were asked to list the subjects which they would like discussed. Acting on these suggestions, the visiting staff was selected according to their particular interest. One week before each meeting all members of the Imperial County Medical Society received personal letters indicating the speaker and subject. Similar letters were sent to adjacent medical groups in Yuma, Arizona, and Mexicali, Mexico. The local newspapers and the local radio stations cooperated in advance publicity. Some time after the program was in effect the local physicians asked for an advance summary of the visiting physician's lecture. This summary was mimeographed and distributed to them, a Spanish translation going to the visiting Mexican physicians.

This service was financed by the Bureau of Maternal and Child Health, State of California Department of Public Health. Each visiting consultant received the same honorarium, as reimbursement for his expenses and at least partial compensation for his time.

It was hoped that the pediatric resident would gain some insight into the problems of medical practice in a rural community, the relationship between the physician in general practice and the medical specialist, the socio-economic structure of a community, and the work of public health agencies. It was also hoped that the local physicians would be continually stimulated to develop an increasing interest in pediatrics. The Imperial County Board of Supervisors agreed to reimburse the Children's Hospital for the services of the residents at the current rate of resident salaries.

The Facilities

A brief description of the parent teaching hospital and the associated county and its facilities seems rather essential.

The Children's Hospital of Los Angeles: This is a modern, 205 bed general hospital, devoted to the care of children up to the age of 14 years. All types of general and special services are available. It is fully approved for general pediatric residency training as well as specialty services. The staff numbers 253 physicians, the majority of whom are either certified by their respective boards or board eligible. They all take an active part in the training programs of the hospital. The hospital is affiliated with the University of Southern California School of Medicine.

Imperial County Hospital: The Imperial County Hospital in the spring of 1948 served as a general hospital of approximately 100 beds, including chronic diseases, a tuberculosis service, and a communicable disease unit. The general pediatric service usually averaged 6 to 10 patients. Severe gastroenteritis, respiratory infections and malnutrition were most commonly encountered. Less frequently seen were other conditions as blood dyscrasias, genitourinary diseases, various surgical conditions, typhoid fever, meningitis. Three to five children with tuberculosis were usually under observation or active treatment. When contagious diseases were prevalent, 3 or 4 children were usually in the communicable disease unit. The newborn service averaged approximately 9 to 12 a month, with an occasional premature.

The laboratory facilities were adequate for routine blood and urine examinations. The usual blood chemical studies could be obtained but not special ones as CO_2, pH, sodium or potassium. Routine roentgenographic studies were easily obtainable.

Treatment rooms and specialized equipment for diagnostic studies and treatment were not available.

Imperial County: The local County Medical Society membership in 1948 consisted of 25 physicians, all general practitioners with the exception of one certified by the Board of Internal Medicine.

Imperial County is an agricultural, rural area about 200 miles from Los Angeles, with an official 1947 population of 65,000 persons. The racial composition of this area is an important factor in its health problems, as ¼ to ⅓ of its people are Mexican or of Mexican parentage. There are, in addition, a few Chinese, Hindus and Filipinos.

Although the rate has been decreasing, for 25 years Imperial County has had the highest infant mortality rate of all counties in California. In 1948 the infant death rate was 56.2 as compared with the state rate of 28.6. In 1950, Imperial, 53.3; State, 26.8. For 1951 complete figures are not yet available, but the provisional infant mortality figures for the first nine months are: Imperial County, 42.9; State, 24.8. Almost half of the deaths during the first year of life occurred over the age of one month, with diarrhea, enteritis, pneumonia and influenza as the leading causes.

Imperial County, situated in the extreme southeastern part of the State, adjoins Arizona on the east and Mexico on the south with no geographic separation from Mexico. It is a low central valley surrounded by rugged, arid mountains, the central feature of the area being the Salton Sea, a salt water inland sea 40 x 18 miles. Since part of this region lies below sea level, the climate is severe, with ranges from 20° to 120° F. Average yearly rainfall is 3 inches.

Evaluation

The project was in operation from the fall of 1948 to the end of June, 1951, approximately three years. The residents were assigned from September until May of each year. Due to the extreme summer heat and to the exodus of workers in the summer months when agricultural work is suspended, the months of June to September were not included in the residents' service.

Twelve senior residents of the Children's Hospital, each previously having at least two year's hospital experience, have participated in this project. Some have found the transition from the highly academic institution to the rural community and its medical practices an easy one; others have found it difficult and frustrating.

During the first year many changes were instituted. The hospital routines for newborns and prematures were modified and improved, as well as the general routines for other pediatric patients. Special treatment facilities were set up and adequate equipment was obtained or improvised so that diagnostic studies and therapy could more easily be carried out. The laboratory cooperated by improving its chemical and bacteriologic diagnostic facilities.

The hospital residents all expressed concern over the lack of the usual close daily supervision and consultation available at the teaching center, but most of them accepted the added responsibilities and provided excellent patient care.

It is difficult to evaluate this service in terms of actual accomplishment, but some pertinent observations may be made.

1. The monthly seminars, conducted by experts in medical fields, were regularly attended by approximately 90% of the physicians in Imperial County, by physicians from Yuma, Arizona, and by Mexican physicians from Mexicali. These physicians actively participated in the sessions with discussion and case presentations. Nurses, other professional personnel, and interested community people also attended most of them.

2. The County Medical Society, having been brought into the planning, continued its intense interest in the plan. The local visiting staff developed a greater interest in the hospital and in the problems presented by its patients. Perhaps one could say that this fact alone must inevitably influence the quality of medical care which the children in this area will receive in the future.

3. The presence of a highly skilled pediatric resident working with the attending staff in the local hospital on a day-by-day basis made it possible to institute in this hospital some of the more difficult therapeutic procedures, to change some of the practices in the newborn nursery and the pediatric ward. This also must have had its influence upon the visiting medical staff.

4. The residents transplanted from a highly specialized metropolitan hospital to a rural general hospital have learned a great deal about the structure of a community, its health problems, its social and economic problems, the professional relationships which must be established, the place of voluntary agencies in the community, and the role of the practicing physician in the local social structure. Specifically, one should mention the fact that probably for the first time the young pediatricians became aware of the basic services which the health department furnishes a community.

5. One very interesting observation which can be made is the fact that the project has focused the attention of a metropolitan teaching center very intimately on the medical problems of a rural area.

6. The project has been the means of bringing many people together—physicians,

nurses, community groups, schools, official and nonofficial agencies—in order to plan together ways to improve the total health of all the children in their community.

7. The value of such a project to the residents participating in it requires more critical appraisal. Was the benefit of two months spent in this rural center commensurate in value to that which would have resulted from spending that time at the Children's Hospital? Are there other means of learning about rural medicine, community health projects and the physician's place in these without sacrificing two precious months of supervised, intensive residency training? Granted, the physicians of the community and the health of the community benefited from the residents' services there, but was the value to the residents enough to justify their assignment, or were we exploiting the residents to test an idea?

These questions cannot be given unqualified answers. Some residents thoroughly enjoyed the experience and were enthusiastic about the value of the service to them. Some were unhappy about the whole thing and felt that their time had been wasted. Others were lukewarm about it, were appreciative of its values but felt that the time could have been spent to greater advantage in the Children's Hospital. This seems to indicate that participants in such a project need to be carefully selected.

8. The drop in infant mortality may be considered as reflecting some of the total community efforts of which this project is only a part. Many other factors undoubtedly affected this decrease.

The question which naturally arose early in the project was how long should this type of service continue? After three years, it seemed that adequate time had elapsed for careful evaluation and demonstration, and accordingly it was decided that the activity be discontinued. On the local level, a great deal of medical benefit had been derived, and from this point of view it would have been very desirable to have continued the program. From the Hospital's point of view it was somewhat difficult to continue the program, although it was recognized that many benefits were derived therefrom. The most serious deficiency in the training of the residents was the lack of daily supervision by a qualified pediatric staff.

However, in order to maintain some continuity in the development of this idea, the Pediatric Consultant with the Bureau of Maternal and Child Health, State of California Department of Public Health, who is also a full time physician on the staff of Children's Hospital, as a part of his service will maintain a close working relationship with the local county medical society and the local hospitals. He has been asked by this group to continue the lectures by the visiting attending staff of the Children's Hospital. In addition he is available for medical consultation to any of the local physicians.

The preceding report is simply a brief description of one method which has been developed by a teaching center to provide continuing medical information to a rural area. It is impossible to state accurately the benefits to each of the many people involved in this type of cooperative effort. However, if the recommendation of the Academy of Pediatrics "to develop systems of decentralized training and rural extension of services so that better care for children may be available in outlying areas" is to be met, this might be considered as one approach to the solution of the problem.

References

1. Park, E. A., in Pediatrician and Public, PEDIATRICS 1:828, 1948.
2. Progress Pediatric Study, American Academy of Pediatrics, Study of Child Health Services, Nov.-Dec., 1948.

SPANISH ABSTRACT

Experiencia Obtenida en Tres Años de Desarrollo de un Programa de Adiestramiento Rural de Médicos Residentes

Los autores describen el programa desarrollado por un centro de enseñanza citadino con objeto de proveer información médica constante a un área rural y en esta forma mejorar la atención médica de los niños de dicha región. Proponen el plan como un posible camino por seguir en el desarrollo de sistemas de adiestramiento decentralizado y de llevar los servicios médicos fuera de los grandes centros pediátricos de enseñanza.

Fundamentalmente el programa consistió en enviar 4 residentes pediátricos por periodos de 2 meses a un hospital rural para desarrollar las actividades médicas necesarias del mismo durante la mitad de este tiempo y el resto para dar conferencias a grupos médicos ó profanos o ayudar técnicamente en los servicios pediátricos de la localidad, de común acuerdo con el delegado de salubridad de la zona.

Aun cuando fué difícil evaluar los resultados obtenidos por el desarrollo del programa fué obvio para los responsables de este artículo los beneficios obtenidos y proponen que debe explorarse este método de enseñanza decentralizada y de extensión de servicios médicos a las zonas rurales.

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EVALUATION OF MEAT IN THE INFANT DIET

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THE importance of protein in the diet of rapidly growing infants and children has long been recognized. Until recently, meat in the diet of infants, particularly in the early months, was not commonly used, milk and milk products being the main source of animal protein.

Leverton and Clark[1] added strained meats to the diets of six week old infants and reported on the effect on red blood count and hemoglobin levels during the eight weeks of the feeding. McQuarrie and Ziegler[2] reported on experimental and clinical studies, comparing the nutritive value of mineral enriched meat with that of whole cow's milk. Sisson, Emmel and Filer[3] reported a metabolic study of premature infants fed meat. They all concluded that meat protein was as well retained and utilized as milk protein, but that strained meats do not contain sufficient calcium and phosphorus to maintain adequate intake for the premature infant. Andelman and co-workers[4] studied the difference in hemoglobin and red blood cell counts in groups of premature infants who were fed breast milk, formula and formula with meat added. They found no significant difference between the groups at 12 weeks of age; however, at 20 weeks of age the infants receiving formula plus meat had a higher hemoglobin concentration than the other two groups studied, and significantly greater than the infants fed formula alone. They state, "The data suggest that meat may contain some hemoglobin-producing substance which is not present in the cow's milk formula even when adequate iron is provided."

Proteins are required for growth and repair of body tissue; for the synthesis of hemoglobin, hormones, complex vitamins and enzyme systems and immune bodies; for the synthesis and maintenance of blood plasma proteins and consequent regulation of blood volume and body protein balance.[5] The protein needs both quantitatively and qualitatively for adequate growth have been derived in great part from young animal and human adult studies. The validity of transposing such data to infants and children has been questioned.[6]

It has been stated that long term studies are needed so that the effect of meat in the infant diet could be measured objectively in terms of height, weight and other variables. Present knowledge of the role of meat in the infant's diet is largely empiric.[7]

The purpose of the study was the careful clinical evaluation of a group of young infants, half of whom were to be fed the standard hospital diet, the other half to be fed the same diet to which strained meat was added as a supplement, in such a quantity as to increase the daily protein intake approximately 25%.

PRELIMINARY SURVEY

Environment: The studies were made in an institution housing approximately 180 presumably normal, healthy children. A majority of these infants were awaiting adoption or foster home care. During

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TABLE 1

SCHEDULE OF DIETARY SUPPLEMENTS

1 Age at Addition	2 Foods Standard Diet	3 Meat Additions (Problem Group)
2 wk.	Orange juice Cod liver oil	1 tbsp.
6 wk.	—	1½ tbsp.
2 mo.	Cereal	1½ tbsp.
3 mo.	Jello Potato	2 tbsp.
4 mo.	Pureed vegetables	2 tbsp.
5 mo.	Pudding	2½ tbsp.
6 mo.	Stewed Fruit	3 tbsp.
7 mo.	Egg and Bread	4 tbsp.

their stay in the hospital, they were housed in small wards according to age, and handling and feeding for each member of the group was almost identical. Common contagious diseases did not occur during the term of the study. All formulae were prepared in a well segregated, glass wall milk laboratory. Formula for each infant was prepared individually and iced immediately in a "walk-in" brine refrigerator. All other foods were prepared in a large modern diet kitchen, separate from the adult kitchen, and under supervision of a trained infant dietitian. Each ward is equipped with a recommended number of reflecting ultraviolet lights. Each ward is equipped with a sink and hand washing facilities, and hand washing between patients is enforced.

Diet: Before undertaking the study, the standard diet of the institution was analyzed at each age level. Observation was made of average intake of various foods at different ages.

Table 1 demonstrates the schedule of dietary supplements in the standard hospital diet. Column 3 shows the schedule for addition of meats for purpose of the study.

Table 2 demonstrates the estimated nutrient values of standard diet, as calculated from average

TABLE 2

ESTIMATED NUTRIENT INTAKE IN STANDARD DIET

Age (mo.)	Total cal.	Protein				Carbohydrate Gm.	Fats Gm.	Iron Mg.
		Cal./kg.	Gm. Total	% Increase	Gm./kg.			
One	441	116	16.0		4.2	41.6	22.4	0.61
	(471)*	(123)	(20.7)	(29%)	(5.4)		(23.6)	(1.38)
Two	587	133	19.7		4.4	61.3	29.0	3.09
	(616)	(140)	(24.4)	(24%)	(5.5)		(30.2)	(4.02)
Three	692	144	27.4		5.7	114.1	61.3	7.64
	(731)	(152)	(33.7)	(23%)	(7.0)		(62.8)	(8.88)
Four	851	157	30.9		5.7	142.7	63.1	8.26
	(890)	(164)	(37.0)	(20%)	(6.8)		(64.6)	(9.50)
Five	1000	158	35.0		5.5	160.7	68.2	11.51
	(1049)	(166)	(42.9)	(22%)	(6.8)		(70.2)	(13.06)
Six	1064	147	36.0		5.0	168.1	71.1	11.82
	(1123)	(156)	(45.3)	(26%)	(6.2)		(73.4)	(13.37)
Recommended Daily Dietary Allowances		100			3.5			6.0

* After addition of meat.

intakes. All infants received equal, and according to current standards, adequate quantities of vitamins A, D and C. Figures in parentheses show quantity and percentage increase in protein after addition of meat to the diet. Percentage increase in daily protein intake in the problem group ranged between 20% and 29%, or an average daily increase of 24%. Standard institution diet exceeded the daily dietary allowances recommended by The Food and Nutrition Board of the National Research Council.[8]

Methods of Study

Observations: "Observation" as used throughout this report designates a complete physical examination, dental survey, weight, body measurements, recording of all illnesses with a description of type and degree, recording number and character of stools, a red blood cell count, white blood cell count and differential count, hemoglobin, total serum protein, serum globulin and albumin, cellular hemoglobin concentration, packed cell volume and a complete urinalysis.

Choice of Subjects: A basic observation was performed on all candidates for the study. If a candidate was free of physical defects, appeared clinically in good health, gave a history of full term birth with a birth weight over 2.3 kg., whose Hgb. was over 10.9 gm./100 cc., the infant's name was recorded on the master record. Cases were assigned alternately to 2 groups, and the examining physician and laboratory staff were notified to continue observations on the infant, without designation as to which group they had been assigned. Formula room and diet kitchen staff and supervising nurses were notified as to the proper dietary group assignment. Infants fed meat were designated as problem group, and those on a standard diet only were designated as control group. Early in the study, infants of various ages were admitted to permit studies on the general acceptability of the meat, its tolerance and effect on stools. As the study progressed, admissions were restricted to infants under 6 mo. of age. After basic observation, an observation was repeated once monthly thereafter as long as the subject remained on the study.

Ward Assignments: Since all subjects were to be observed for occurrences of infection, it was important that a plan of bed assignment be outlined and adhered to. This plan must assure that if any accidental exposure to infection should occur there would be comparatively equal exposure to both problem and control cases in the involved area.

Bed assignments, made by the nursing supervisor, were by narrow age ranges. Each ward housed 6 to 10 infants of similar ages, with problem and control cases in alternating beds. Cases moved from ward to ward with age progression, maintaining the age level for the respective wards as well as the balance of cases. Nursing personnel assigned to designated wards cared for all the needs of all the infants in their respective wards.

Method of Feeding: Up to approximately the age of 3 mo., strained meat was placed in the formula in the milk laboratory according to written directions on each child's diet card. Meat was distributed equally throughout the bottles comprising the 24 hr. formula. Formulae were prepared under cold aseptic conditions and immediately iced. Individual bottles were warmed to 37°-48° C. in a water bath just before feeding. With this method of handling, coagulated protein was not encountered. Where infants were fed by spoon, the cans were cleansed, opened and placed in a warm water bath until feeding was completed.

Meat was fed 6 days a week, Sunday excepted. Each subject in the problem group was fed the same kind of meat on the same day. Six types of meat (beef, liver, lamb, veal, beef heart and pork) were fed in succession, but in no scheduled order.

Laboratory Methods: Bloods for each observation were obtained at 30 day intervals, at approximately the same time of day. All blood specimens were obtained from an incision in the heel which provided free flowing blood. Throughout the study all specimens were collected, and all laboratory determinations were performed by the same personnel. Problem and control subjects were assigned to the study simultaneously in small groups so that blood studies would be done on the same day for the purpose of minimizing the effect of climatic changes.

Hemoglobin determinations were performed on the Evelyn photoelectric colorimeter.[9-10]

Cell volume and red cell counts were made on the Evelyn photoelectric colorimeter according to published methods.[11]

Total proteins were performed on the Kagen proteinometer.[12]

Albumin in the serum was determined by the method of Kingsley.[13]

Globulin in the serum was calculated by subtracting the albumin from the total protein.

Leukocyte and differential counts were made by ordinary accepted procedures.

Urines were examined for specific gravity, albumin, sugar, acetone and chemical and microscopic examination for presence of blood.

Physical Measurements: Body length was determined by placing the infant in a cradled measuring rack, with a sliding foot board. Head and chest measurements were made with a flexible metal tape. All physical examinations, measurements and recordings of illness were done by one physician (GSG) for the entire period of the study.

Recording of Illnesses: At each monthly observation, the examining physician recorded by degrees all upper respiratory infections and gastrointestinal disturbances that had occurred during the preceding month. Rigidly defined standards for the degree of illness were set up and followed closely in the recording.

Analysis of Results

During the two years of the study, 28,944 monthly observations were made on 904 infants and children. As anticipated, a large number of cases were lost after various periods of study due to placement or adoption. Since most of the factors studied change rapidly in very young children, and at rates that vary with the age of the children, it was necessary to restrict comparisons to groups of children who fell within relatively narrow age levels. While many remained under observation for as long as 12 months, the number in each age group remaining longer than six months was too small to be significant. For the purpose of the analysis, only those cases that were observed for a minimum of two months, and a maximum of six months were included. The number of infants fulfilling these criteria for analysis totaled 303; of these 133 were in the control and 170 in the problem group. The age of the children when placed in the study group and the number used for statistical tabulation included:

Months of Age	Control	Problem
0 to 1	39	24
1 to 2	31	41
2½ to 4½	18	24
4½ to 7½	10	9
7½ to 11½	13	24
11½ to 15½	11	18
15½ to 18½	4	14
18½ to 21	7	16

Ninety-one per cent of the 303 infants remained under observation for three full months or more, 63% for four months or more.

For the sake of brevity, the results of most of the observations are summarized. Graphs and tables are here used only to demonstrate the more significant findings.*

Weight: Each of the groups was tested, using the "t" test[14] for the difference between means, and it was found that there was no significant difference in the starting weight of the problem group as compared to the starting weight of the control group. The average weight gain per child receiving the meat supplement exceeded that of the controls in 5 of the 8 groups, and equalled it in one other. Only the problem infants in the two oldest groups, 15½ to 18½ and 18½ to 21 months, failed to gain weight faster than the controls. For these older groups, however, the period of study covered a shorter period of time.

* Details of statistical analyses, tables and graphs are available on request to the authors.

Height: The average height increase was greater for the problem group than for the control group, in the groups that started on the study between birth and two months of age. However, the amount of difference was not great enough to be statistically significant ($P > 0.05$). Comparison of the average increase in height in the other age groups studied demonstrated no apparent difference.

Head and Chest Circumference: Graphs constructed for these measurements demonstrated no essential difference between problem and control cases in any of the age groups.

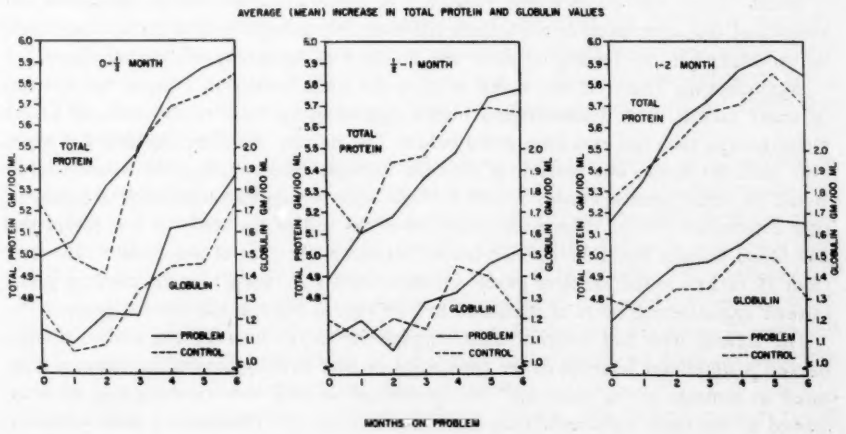
Tooth Eruption: Analysis of the time of tooth eruption indicated no essential difference between the problem and control groups.

Hemoglobin: Because of the size of the sample, and the wide range of fluctuation between hemoglobin values, the median average was used as the more suitable measure.[15] It was noted that the ranges between which the values fluctuated were smaller for children included in this study, both control and problem, than has been reported for infants of this age.[16] The quartile deviation,[17] measuring dispersion around the median, showed that the hemoglobin of the problem group deviated less from the median than did that of the control group, the difference being great enough to have statistical significance. The variance ratio[18] yielded a "P" of less than .05.

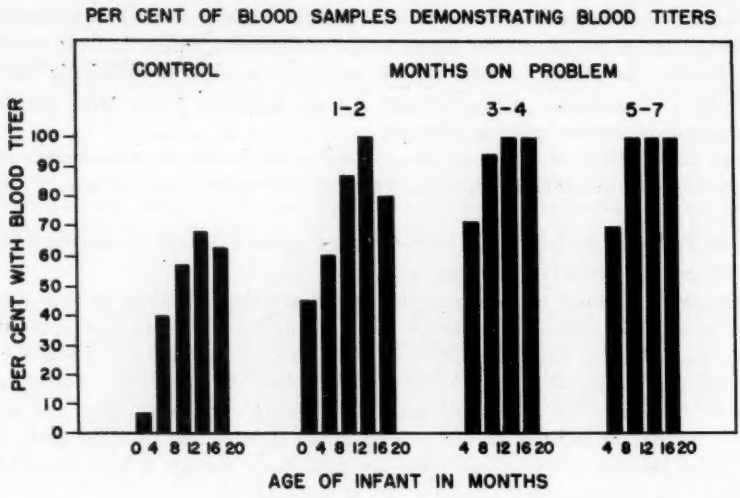
In addition to the fact that there was lesser variation in hemoglobin levels, the younger children who received meat showed less of a physiologic drop and a faster return to normal hemoglobin values.

Corpuscular Hemoglobin Concentration: Analysis of the average corpuscular hemoglobin concentration for the various groups failed to show any significant variation, either within the groups or between the groups.

Total Protein: The average (mean) increase in total protein values for the younger age groups is demonstrated in graph 1. It is recognized that the total protein of the newborn begins to drop immediately after birth and then begins to rise again during the second or third month of life. The control group showed the usual physiologic drop, while the problem group showed a continuous rise in total protein, the rate of the rise exceed-



GRAPH 1



GRAPH 2

ing that of the controls. Similar graphs constructed for the various age groups over two months demonstrated no significant difference between the control and problem groups.

Albumin and Globulin: Average total protein and globulin levels are shown on graph 1, and show higher values for the problem group in both total protein and globulin. There was little significant variation between the two groups in the albumin levels.

Blood Counts: Packed cell volume, red and white blood cell and differential counts were analyzed. Graphs constructed for these factors indicated no essential difference between problem and control cases in any of the age groups.

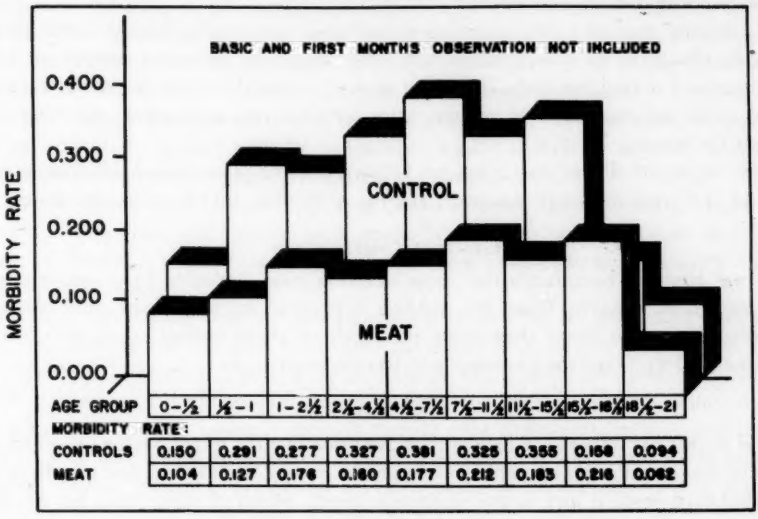
Urinalysis: Routine complete urinalyses were done on all cases. There were no findings that indicated any adverse effect from feeding meat to the young infants.

Stools: There was no increased frequency of stools apparent and no change in consistency or character noted in the infants fed meat. No gastrointestinal disturbances could be contributed to the feeding of meat and no signs of sensitivity to meat developed.

Agglutinating Titers: It was noted early in the study, purely by chance, that the sera of many infants were demonstrating higher agglutinating titers against cells of known blood groups, than had ever been noted before. The authors, therefore, decided that whenever sufficient serum was remaining after the monthly blood studies, the infant's serum would be tested against known A and B blood cells for agglutination and, if present, a titer determined. When these were compiled at the end of the study, it was found that 285 blood samples had been tested from 60 infants in the control group, and 216 tested from 59 infants in the problem group. Of these, 153 (or 75.5%) in the problem group showed agglutinating titers as compared to 115 (or 40.4%) in the control group.

The infants who had received meat supplement for as little as one to two months showed a significant increase in the percentage of sera with agglutinating titers, as compared to controls of the same age. The percentage of sera with agglutinating titers increased as the meat supplementation continued (graph 2). There was a direct relationship between the height of the agglutinating titer and the length of time the child received meat. Not only did more children show agglutinating titers, but the agglutinating

MORBIDITY RATES OF INFANTS ON MEAT-SUPPLEMENTED AND CONTROL DIETS



AGE GROUP	0–½	½–1	1–2½	2½–4½	4½–7½	7½–11½	11½–15½	15½–18½	18½–21
MORBIDITY RATE:									
CONTROLS	0.150	0.291	0.277	0.327	0.381	0.325	0.355	0.158	0.094
MEAT	0.104	0.127	0.176	0.180	0.177	0.212	0.185	0.216	0.062

GRAPH 3

titer values were higher in bloods drawn from the children who had received meat supplements over longer periods of time.

Illnesses: The only illnesses which occurred during the period of study were upper respiratory infections and gastrointestinal disturbances. These were evaluated as to kind, number and degree of severity. Basic and first month observations were excluded in order to eliminate the influence of care or contact prior to being placed on the problem. Statistical tests were applied to determine whether there was a significant difference between the two groups as to number of children who had illnesses. One hundred-six (or 64.3%) of the 165* infants fed meat had one or more illness, while 105 (or 79.5%) of the 132† infants in the control group were ill one or more times. There were significantly fewer children in the meat-fed group who had illness, the "t" value for the difference being 2.97. The chance of drawing two samples from the same universe with differences this great is less than 3 in 1000.

Since the number of children on the problem vary from one period of observation to another, a morbidity rate was established by computing the ratio of illnesses to observations. Graph 3 compares, by age groups, the morbidity rate of the children in the problem and control groups. The morbidity rate for the children fed meat was lower than for the control group in each age group except 15½ to 18½ months. The morbidity rate of the children in the meat-fed group was 0.157 compared to a morbidity rate of 0.262 for the control group, or a 40% lower morbidity rate for the problem group as compared to the control group. The probability of differences this great drawn from the same universe for samples the size of these is less than 1 in 10,000.

A statistical comparison was made of illness by seasons. The highest morbidity rates

* Record of illness lost in 5 cases.

† Record of illness lost in 1 case.

in both groups occurred from December to March and the lowest from June to September in both years of the study. The control group showed a greater fluctuation of morbidity rate with the change in seasons.

Analysis of morbidity rates according to wards was not possible because of the regular, periodic change in ward assignments with progressing age. No major outbreak of infection occurred during the study and minor seasonal outbreaks in the respective wards offered equal exposure to both groups, since alternate bed assignment was maintained within the wards.

The degree of illness was compared. The number of more serious illnesses in both control and problem groups was small and the proportion did not differ significantly.

General Observations

It was observed consistently that those receiving meat seemed to have greater vitality and slept more soundly. When the children were given inoculations or were restrained for blood counts or blood chemistries, the meat-fed group seemed to cry with less intensity and to withstand the procedure with less emotional upset.

Discussion

It is of primary importance for optimum nutrition that the infant diet be so constructed that the various nutrients be ample and proper for energy, maintenance and growth needs. The standard hospital diet in this institution over a period of many years has not only met but exceeded the accepted requirements[8] of the various food factors. The results observed after adding meat proteins to what was assumed to be an adequate infant dietary brings out certain facts which should lead us to assess our present standards more carefully, in striving for the optimum in infant nutrition.

Weight gain in the meat-fed group was significantly increased, with the greatest increment occurring in those fed meat under 2 months of age. There was likewise a slightly greater average increase in height in the same group. The hemoglobin levels were slightly improved in the problem group, the greatest effect again being noted in the children who started the feedings under 2 months of age. Total protein levels were significantly influenced in the children under 2 months, with virtual elimination of what heretofore had been regarded as a physiologic drop. The increase in protein values appeared to be comprised to a greater degree by the globulin fraction.

It may be said that although the standard hospital diet for the first 2 months of life exceeded present recommended requirements, in view of the above findings, supplementation of the diet with meat proteins produced a state of improved nutrition.

The incidence of illness, as compared in the two groups, during the two years of the study was greater in the control group irrespective of seasons, or manner of analysis. With a total of 2,273 observations on 297 subjects, the meat-fed group had a 40% lower morbidity rate.

It is of interest to note that in those children first fed meat after 2 months of age, and after their diet had already been supplemented with other foods, no significant difference was noted between the problem and control groups in body measurements, total protein, albumin or globulin fractions, or hemoglobin levels. There was a slight difference in average weight gain, favoring the meat-fed group. Although the measurable physical differences between the groups over 2 months of age were negligible, the very considerable difference in the rate of infections between the problem and control subjects through the age groups above 2 months is significant and deserving of consideration.

Madden and Whipple[19] state that "Although acquired resistance enhances resistance to infections against which natural resistance may be inadequate, this does not mean that the value of the latter is to be underestimated nor that it cannot be increased by optimal nutrition. The increasing emphasis upon protein metabolism in relation to infection and resistance, therefore must be evaluated with respect to both types of immune processes." Information derived from amino acid analysis, electrophoresis and biologic technics indicates that normal serum globulin and antibody globulin are essentially similar types of protein, that diet regulates globulin production equally as well as albumin, indicating that globulin synthesis is basically a nutritional problem.[19]

Cannon[20] states that "Inasmuch as experimental evidence indicates that globulin production is dependent upon the intake of amino acids and is impaired by an inadequate intake of dietary proteins, it also follows that antibody production must similarly depend upon protein intake."

Although the standard hospital diet provided both an adequate caloric and protein intake, it is apparent that resistance to infection was enhanced in the subjects fed meat. These findings might be clarified in part by the experiments of Cannon[20] who states that "Caloric intake determined the efficiency of protein synthesis . . . with an adequate caloric intake, the efficiency of protein synthesis depends directly upon protein quality and quantity . . . deficiency of only a few milligrams per day of a particular essential amino acid hampers effective protein synthesis, despite the adequate intake of all the others. If a complete tissue protein is to be synthesized, all the essential amino acids which are to enter into the process must be simultaneously available, and in adequate amounts and proportions one to another during the act of synthesis. In other words, unless a tissue protein can be synthesized at once and completely, it may not be synthesized at all." Similar reports by various investigators of protein metabolism establish quite firmly the fact that all essential amino acids in the diet must be present simultaneously and in adequate amounts for complete synthesis.

The sera of the meat-fed group demonstrated agglutinating properties against cells of known blood groups, in greater number and with higher agglutinating titers than the control group. The possible relationship between these findings and the smaller rate of infection in the problem group suggests a correlation worthy of further investigation.

The above findings suggest that we review our present concepts of protein needs in the infant diet in striving for the optimum in infant nutrition.

Summary

A commercially prepared lean meat was fed to young infants as a supplement to a diet already adequate in all food factors.

In those infants first fed meat under 2 months of age, there was improvement in physical growth as determined by weight and height measurements. The same group demonstrated an improvement in hemoglobin levels; the elimination of the physiologic drop in total protein levels of the serum, with a prompt sustained rise in values, the greater part of which was composed of the globulin fraction.

In those infants first fed meat after 2 months of age, there was a slight improvement in average weight gain, but no significant difference was noted in other body measurements, total protein, albumin or globulin fractions, or hemoglobin levels.

Illness rates for the two years of the study demonstrated a 40% lower morbidity rate in the meat-fed group as compared to the control group.

In striving for the optimum in infant nutrition protein requirements should be evaluated both quantitatively and qualitatively.

ACKNOWLEDGMENT

The authors are indebted to Cecelia M. Kortuem, R.N., medical technologist in charge of the laboratories, whose technical assistance made this study possible; to Elizabeth Adles, Ph.B., M.B.A., Supervisor of Statistics and Research, Public Assistance Division, Cook County Department of Welfare, for her invaluable assistance in the statistical analyses; and to The Daughters of Charity for their deep interest and excellent nursing and diet supervision.

REFERENCES

1. Leverton, R. M., and Clark, G., Meat in diet of young infants, J.A.M.A. **134**:1215, 1947.
2. McQuarrie, I., and Ziegler, M. R., Nutritive value of mineral-enriched meat and milk, PEDIATRICS **5**:210, 1950.
3. Sisson, T. R. C., Emmel, Anne F., and Filer, L. J., Meat in diet of premature infants, PEDIATRICS **7**:89, 1951.
4. Andelman, M. B., Gerald, P. S., Rambar, A. C., and Kagan, B. M., Early feeding of strained meats to prematurely born infants, PEDIATRICS **9**:4, 1952.
5. Borden's Review of Nutrition Research, New York, The Borden Company, 1945, vol. 6, p. 10.
6. Levine, S. C., Nutrition in Pediatrics, edited by M. Sahyun, New York, Rheinhold Publishing Company, 1948, Chap. 10.
7. Editorial, J.A.M.A. **135**:162, 1947.
8. Recommended Daily Dietary Allowances, National Research Council, Reprint and Circular Series, No. 129 (Sept. 1) 1948.
9. Evelyn photoelectric colorimeter, J. Biol. Chem. **115**:63, 1936.
10. Kortuem, C. M., Red blood cell counts: Photoelectric colorimeter vs. hemocytometer with correction factor for abnormal cells, Am. J. M. Technol. **6**:5, 1940.
11. Kortuem, C. M., Modernizing color and volume index, Am. J. M. Technol. **9**:1, 1943.
12. Kagan, B. M., Elimination of standards and nomograms in determination of whole blood specific gravity by falling drop technique, J. Lab. & Clin. Med. **26**:1681, 1941.
13. Kingsley, G. R., Report of method for separation of serum, albumin and globulin, J. Biol. Chem. **133**:731, 1940.
14. Croxton, F. E., and Cowden, D. S., Applied General Statistics, New York, Prentice Hall, Inc., 1947, p. 330.
15. Ibid., p. 208.
16. MacFate, R. P., and Levinson, S. A., Clinical Laboratory Diagnosis, Philadelphia, Lea & Febiger, 1943, p. 801.
17. Croxton and Cowden,[14] p. 237.
18. Ibid.,[14] p. 347.
19. Madden, S. C., and Whipple, G. H., Plasma proteins: Their source, production and utilization, Physiol. Rev. **20**:194, 1940.
20. Cannon, P. R., Antibodies and protein-reserves, J. Immunol. **44**:107, 1942.

SPANISH ABSTRACT

Evaluación de la Carne en la Dieta del Lactante

Se hizo una evaluación clínica cuidadosa de un grupo de lactantes, alimentándose a 133 de ellos con la dieta standard del hospital, que demostró ser adecuada en todos sus factores nutritivos, y se compararon con 170 que fueron alimentados con la misma dieta pero adicionada de un preparado comercial de carne como suplemento para aumentar la ingesta protéica diaria en un 25% aproximadamente.

Una véz al mes se hicieron en cada niño las anotaciones siguientes: exploración física completa, examen dental, peso, medidas antropométricas, registró de todas las enfermedades con su variedad e

intensidad, registro del número y caracteres de las evacuaciones, cuenta de eritrocitos, leucocitos y sus variedades, hemoglobina, proteínas totales del suero, seroglobulina y seroalbúmina, concentración eritrocítica de la hemoglobina, hematocrito y análisis completo de orina.

En aquellos lactantes en que se inició la alimentación con carne cuando tenían menos de 2 meses de edad, hubo una mejoría en el crecimiento físico como se determinó por el peso y la estatura. En el mismo grupo se demostró mejoría en los niveles de hemoglobina, ausencia de la caída fisiológica de los niveles de las proteínas totales del suero con una elevación rápida y sostenida y valores promedio mas altos de proteínas totales y de las globulinas.

En aquellos lactantes que se alimentaron con carne por primera vez cuando tenían más de 2 meses de edad hubo una mejoría ligera en el promedio de ganancia de peso, pero no se notó diferencia de significación en otras medidas del cuerpo, proteína total, albúmina globulina ó niveles de hemoglobina.

Los coeficientes de enfermedades de los dos años del estudio demostraron un coeficiente de morbilidad 40% más bajo en el grupo alimentado con carne en comparación con el grupo control.

En el esfuerzo por obtener la nutrición óptima del niño los requerimientos de proteínas deben evaluarse tanto cuantitativa como cualitativamente.

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PSYCHOGENIC MEGACOLON MANIFESTED BY FECAL SOILING

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Chicago

SWENSON'S[1] report of the surgical relief of symptoms in 82 cases of congenital aganglionic megacolon (Hirschsprung's disease) has reawakened interest in this disorder. In the past, Hirschsprung's disease and megacolon have often been considered to be synonymous. Megacolon is only a descriptive term, however, and there are several etiologic mechanisms for its production. The availability of an effective surgical approach emphasizes the importance of a precise etiologic diagnosis in each patient if ill-advised surgery is to be avoided.

Bodian et al.,[2] Lee et al.[3] and Lee and Bebb[4] have presented excellent reports in which patients with megacolon of various types are grouped according to their clinical and radiographic findings. "Functional" megacolon has been recognized as a distinct entity by them, but its psychogenic origin has not been clearly recognized. The present authors, therefore, consider it important to report six cases of psychogenic megacolon in which surgery is contraindicated. Criteria for the clinical diagnosis of this condition and a classification of megacolon will also be presented.

CASE MATERIAL AND METHOD OF STUDY

Six patients with megacolon were studied in whom an aganglionic segment was excluded on the basis of history, physical findings and fluoroscopy using Neuhauser's technic.[5] The psychiatric problems of these children were investigated entirely within the pediatric setting. For brevity only a single representative case report is presented.

Case 2: E.G., white male, was admitted to Research and Educational Hospitals at 11 yr. of age because of fecal soiling.

Patient was a full-term baby. He remained in the hospital during the 1st 3 to 4 wk. of life because of jaundice, but the specific diagnosis made at that time was unknown. After he was brought home, he experienced painful, blood-streaked, infrequent stools which suggested the presence of anal fissures. He was bottle fed because breast feeding was impossible after the prolonged neonatal hospitalization. At times he was held by the mother or maternal grandmother during feedings, but frequently he was not picked up, and the bottle was simply held for him.

At 1 yr. of age bowel training was begun by placing the patient on a small "potty" chair. Occasionally he had bowel movements there but usually he passed them in his diapers. Soon his mother began to spank him for soiling. When bowel control did not occur as a result of this, she tried coaxing, nagging and bribing in addition. As a result, the child frequently sat on the chair and strained but continued to have most of his bowel movements in his pants. At the end of the 2nd yr., no bowel control was apparent, and a physician advised the use of laxatives and enemas as a means of training. Enemas were begun and given almost daily. The child fought these by screaming and kicking and it was difficult to insert the nozzle because "he would tighten up." By the latter part of 3rd year, the patient was sent to an outside toilet for defecation, but he usually lied about having stools there and soiled later. Bladder control was completed by the end of the 2nd year, but bowel control was never attained. No subsequent enuresis appeared; however, fecal soiling persisted to the present admission.

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(Received for publication April 30, 1952.)

Patient was the illegitimate son of a 19 yr. old mother whose pregnancy was deeply resented by the maternal grandfather. After the patient's birth, the mother lived in the grandparents' home, and much of the responsibility for the baby's care was assumed by them. The mother married when the patient was 6½ yr. of age. The child continued to live with the grandparents, however, until the grandfather's death 1 yr. later. The patient then moved to the mother's home where his soiling became a source of continuous controversy between the mother and step-father. The mother put thick padding in the patient's pants when he went to school. He resented this so much that he ran away from home a number of times and was beaten severely for it by his step-father. In spite of these difficulties the patient did very well scholastically. At the age of 10¾ yr., he remained out of the home for a period of 3 mo. after running away and lived during this time with a family which had befriended him. It was the mother in the latter home who finally brought him to the hospital for medical care.

The patient's own mother was an ineffectual, apathetic person of 31 yr. who weighed less than 41 kg. and had been physically weak from earliest infancy. She seemed inadequate both physically and emotionally to fulfill a maternal role, and the patient stated that he had always regarded her more as a sister than a mother. She professed a desire to have the patient at home with her but had made no attempt to induce him to return to her prior to his hospitalization. In the hospital she tried to bargain with him by offering to leave her husband if he would return to her.

Physical Examination: Patient weighed 28.9 kg. and was 133.5 cm. tall. These values were below the 10th percentile rankings on the Stuart-Meredith tables. His appearance was strikingly immature and there were no pubertal changes. Large fecal masses could be palpated readily on L side of the abdomen. No obstructive lesions were felt on rectal examination, the anal sphincter had a normal tonus, and the rectum was packed with feces to the anus.

Laboratory Examination: Neuhauser's fluoroscopic technic[8] failed to reveal a spastic segment of rectosigmoid. On barium enema a megacolon was seen which began at the anus. The colon was so markedly redundant that incomplete rotation was suspected initially but not confirmed. Normal haustral markings were present in the ascending and transverse colon.

Course in the Hospital: There were occasional episodes of abdominal colic. All stools were passed when the patient was standing or lying supine in bed, and the toilet was never used for defecation. Soiling was continuous throughout hospitalization. The patient had a marked fecal odor which failed to disturb him. His behavior was immature and he preferred a severely deformed 8 yr. old child as his closest friend. The patient used the younger child to express some of his hostility, but was always overtly obedient and unusually conforming. He seemed to have a complete lack of interest in sexual matters, and masturbation was not noted before or during hospitalization. The patient spoke about his symptoms and family situation without emotion or feeling. At the time of this report he has been hospitalized for 3 mo. without improvement.

Results and Discussion

The hospital records of the six patients were reviewed to determine the features which were common to most of the children and which differed from those of aganglionic megacolon. The findings provided adequate evidence, the authors believe, for the psychogenic origin of the megacolon in these patients. Several historical and clinical features were sufficiently striking to permit criteria to be established for the diagnosis of psychogenic megacolon without the necessity of a detailed psychiatric history. On the basis of these criteria clinicians can readily segregate the nonsurgical from the surgical cases of megacolon. The important features of the records of the six patients are summarized in table 1.

Fecal Soiling (encopresis): Fecal soiling was the admitting complaint in 5 of the 6 patients. In the sixth it developed later. This important finding almost immediately differentiated psychogenic from aganglionic megacolon because encopresis usually does not occur in the latter disease. The children all seemed unaware of their fecal odor and continued to soil in spite of unmerciful teasing by other children. Enemas or large spon-

TABLE 1
ANALYSIS OF CASES

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Encopresis	+	+	+	+	+	+
Age at onset	3 yr.	2 yr.	5 yr.	3½ yr.	8 yr.	3 yr.
Coercive bowel training	+	+	+	+(?)	+(?)	+
Attainment of bowel training	−	−	−	+	+	+
Refusal to defecate on toilet	+	+	+	+	+	+
Urination on toilet	+	+	+	+	+	+
Defecation when standing or supine	+	+	+	+	+	+
Visible effort to retain stool	+	−	+	+	−	+
Abdominal pain	+	+	−	−	−	+
Vomiting	−	−	−	−	−	−
Periodic voluminous stools	+	−	+	+	+	+
Feces-filled rectum	+	+	+	+	+	+
Absence of spastic segment on fluoroscopy	+	+	+	+	+	+
Duration of disease at time of admission	1+ yr.	9 yr.	4+ yr.	1½ yr.	2 yr.	6 mo.

taneous defecations were usually associated with temporary improvement in the encopresis.

Age at Onset: The exact age of the children at the onset of the disease was not definitely determined in most instances because of the insidious nature of the disease. If the appearance of encopresis was assumed to correspond to the time of onset, however, the disease began from the 3rd to the 9th years of life in the six patients. No features of the disease were present in the neonatal period in any of the patients. Symptoms appeared after the time at which neuromuscular development usually permits voluntary control of the external anal sphincter and suggested that inhibition of defecation was important in psychogenic megacolon.

Coercive Bowel Training: A definite history of coercive bowel training was elicited in 4 of the authors' 6 patients. In Case 1 it was accomplished through enemas from the second month of life; in Case 2 through early training, punishment and enemas; in Case 3 also through early training, punishment and enemas; and in Case 6 through early training and physical restraint on the toilet. In Case 4 there was intense concentration on bowel functioning after the onset of encopresis and suggestive evidence that a high love premium was placed on bowel performance prior to that time. In Case 5 the history was not definite, but the mother's statement that the child had been bowel and bladder trained shortly after a year of age suggested that training was coercive.

Huschka[6] considers training methods to be coercive if they are undertaken before neuromuscular development permits voluntary control or if training methods are destructive. As examples of the latter she lists the following: frequent and marked employment of shame; punishment for failure to comply; use of suppositories as educative aids; rigidity of toilet schedule; unduly frequent placement on the toilet; placing a high love premium on perfect performance; refusing to place the child on the toilet until he expresses his wants in speech even though he has appealed for help; mechanical measures such as strapping the child to the toilet. She found that it was often more difficult to elicit a history of training technics than it was to gain a sexual history of the child. Perhaps this accounted for the authors' failure to obtain an adequate history of training methods in two cases.

Attainment of Toilet Training: In three of the patients bowel training, in the usual sense of the word, was never accomplished. In the other three it was accomplished at the usual time but disappeared after a variable period. Case 4 had used the toilet for defecation for 1½ years; Case 5 for 6½ years; Case 6 for one year prior to the onset of encopresis. Once encopresis began, all the children had a lapse in bowel training and passed the majority of stools in their clothing, though they invariably continued to urinate on the toilet. Cases 1 and 6 developed nocturnal enuresis and Case 4 had both nocturnal and diurnal enuresis.

Defecation in the Standing or Supine Position: Concomitantly with the onset of encopresis all the children passed stools in either the standing or supine positions, and soiling often occurred at night when the patients were recumbent. Bodian et al.[2] described this feature of the disease and felt that the extended position facilitated defecation. This is contrary to available information concerning the physiology of defecation. The squatting position with adequate support for the ischial tuberosities places the accessory muscles of defecation at a mechanical advantage and supplies a fulcrum action for the levator ani muscles. An extended position is assumed when an individual attempts to withhold the stool voluntarily. In Case 4 the patient secretively went behind furniture, became flushed, and stood with the legs held tightly together. Three other patients gave a similar history. This behavior could not be interpreted as effective straining, because the patients avoided the squatting position; rather, inhibition of defecation was suggested.

Abdominal Colic: Cramping abdominal pain occurred in three patients; however, none of them gave a history of vomiting, and intestinal obstruction was not suggested at any time. Although a precise interpretation of physiologic events was impossible, it is conjectured that these patients may be uncomfortable or in pain while inhibiting peristaltic urges to defecate. Fecal soiling in these patients, therefore, may indicate that such inhibition has not been entirely effective. Five of the six patients demonstrated the integrity of bowel function by passing voluminous stools either spontaneously or in response to enemas.

Abdominal Palpation: Feces were palpable abdominally at some time during the course in all patients, but the extent of the fecal masses was variable even without therapy and depended upon the frequency and volume of defecation.

Rectal Examination: In all patients the anal canal was short and the rectum was packed with feces.

Fluoroscopy: None of the patients demonstrated a spastic segment of rectum or rectosigmoid on fluoroscopy by Neuhauser's technic[5] and dilatation extended to the anus in every case. Marked redundancy of the colon was a uniform finding and at times suggested an incomplete rotation or malrotation of the bowel. The elongated sigmoid and descending colon often extended into the right upper quadrant.

Bodian et al.[2] have described the fluoroscopic findings in their patients. These findings could be grouped into two general categories. In one group the rectum and sigmoid had the appearance of a dilated, pear-shaped, unilocular chamber. The involved segment frequently extended from the anus to the xiphoid on the roentgen film, and a definite point of demarcation between normal and abnormal bowel could be seen. In the other group a long segment of the distal bowel presented a "tubular dilatation" which extended well into the proximal colon; the abnormal segment in these patients was smaller in diameter than in the former group, and the demarcation between dilated and normal bowel was less well defined.

Marked redundancy of the colon in these patients might predispose to constipation in itself by enhancing stasis and by increasing the absorptive surface to which the stool is exposed in the distal bowel. It is the authors' thought, however, that the redundancy is the result of chronic constipation rather than the cause of it. In one patient, not reported in this series, redundancy recurred after two feet of the colon were removed surgically prior to admission to this hospital.

Course: The physical condition of the six patients presented remained excellent throughout the course. In Case 2 the disease had existed for approximately nine years without systemic symptoms. In the other five patients the disease had run a benign course for 6 months to 4 years. Physical measurements were in the low percentiles in Cases 1, 2 and 4 but this was attributed to associated feeding disturbances.

In Bodian's[2] group of 34 similar cases no deaths occurred; however, 11 of 39 patients with aganglionic megacolon died. Megacolon of psychogenic etiology, therefore, may be assumed to be a relatively benign condition from the standpoint of survival while untreated neurogenic megacolon carries a high mortality.

Observations of Psychopathology: The majority of the children were unusually obedient and conforming and were often neat in all spheres except the gastrointestinal. School age children usually performed well in their studies and were often favorites of the teacher. Most of the children controlled all manifestations of hostility and aggressiveness, except for their soiling, and favorably impressed adults. They usually related poorly to children of their own age. Their attitudes were often stoic and they seldom displayed overt emotion. The two prepubertal children, Cases 2 and 5, showed no interest in sexual matters or evidence of sexual conflict. All the children were strikingly immature in appearance.

The mothers of these patients seemed incapable of expressing genuine warmth or feeling. In 5 of the 6 patients the first three months of life were characterized by painful gastrointestinal experiences (enemas, anal fissures, colic), and a definite impression was obtained from the histories that the only consistent cutaneous stimulation and attention which the patients received in early life occurred in association with diaper changes. Bowel training was coercive and defecation became a mixed experience of physiologic relief and discomfort. Control of defecation probably was present in all the patients in spite of the soiling; this was suggested by the extended position which these children assumed in defecating and by the fact that symptoms began only after neuromuscular development had progressed to the point at which voluntary retention of feces was possible. When the stool was expelled entirely at one time, it was usually voluminous; soiling thus may have represented an "escape" of the stool. The patients must have gained secondarily by this, because they continued to soil in spite of punishment, teasing, criticism, and forced cleansing of their own clothes. All the children seemed to be oblivious of their fecal odor and the contact of the stool with the perineum and buttocks.

Comment

Psychogenic Megacolon: Fecal soiling is the major complaint in patients with psychogenic megacolon and should always direct attention to the possibility of this disease. Additional characteristics which were found to be useful clinically in differentiating this group of patients from those with aganglionic megacolon were as follows: onset in the second year of life or later, infrequent use of the toilet for defecation, defecation in the standing or supine positions, inhibition of the stool, periodic voluminous stools, absence

of episodes of intestinal obstruction, a feces-packed rectum, absence of a spastic segment of rectum or rectosigmoid on fluoroscopy using Neuhauser's technic and a relatively benign course.

An intensive study of the psychodynamics in patients with psychogenic megacolon is indicated. Treatment in the pediatric setting was found to be relatively ineffective in these patients and specific and deeper psychotherapy would seem to be the only effective therapeutic approach.

Neurogenic Megacolon: Hirschsprung's disease was the term formerly applied to this group of patients. As a result of the work of Tiffin et al.,[7] Whitehouse and Kernohan,[8] Zuelzer and Wilson,[9] Bodian et al.,[2] Swenson et al.[5] and Hiatt,[10] it is now believed that the disease has a neurogenic origin and results from an absence of ganglion cells in the myenteric plexus of the distal bowel. Swenson, Rheinlander and Diamond[11] and Hiatt[10] studied the area of defective innervation by kymography and found that it failed to transmit peristaltic waves, remained constricted, and acted as an area of partial intestinal obstruction. As a result, dilatation, hypertrophy and fecal retention occurred proximally. The present authors employ the term neurogenic megacolon for this disorder to indicate its genesis.

Following the development by Neuhauser of a diagnostic, radiologic technic, Swenson

TABLE 2

DIFFERENTIATING FEATURES

Psychogenic megacolon	Neurogenic megacolon
Admitting complaint: Fecal soiling	Admitting complaint: Constipation without fecal soiling
Age at onset: 2nd year or later	Age at onset: Birth or first weeks of life
History: Coercive bowel training Toilet training successful at some time or always unsuccessful Infrequent use of toilet after onset Defecation in standing or supine position Inhibition of stool Colicky abdominal pain Periodic voluminous stools	History: Lack of coercieve bowel training (enemas only for true obstipation) Toilet training usually successful Use of toilet for defecation Defecation in sitting position Rarely abdominal pain Pellet-like or ribbon-like stools
Past History: No episodes of intestinal obstruction	Past History: Frequent episodes of intestinal obstruction
Physical examination: Feces-packed rectum	Physical examination: Empty rectum
Fluoroscopy (Neuhauser's technic): Absence of spastic segment of rectum or rectosigmoid	Fluoroscopy (Neuhauser's technic): Presence of spastic segment of rectum or rectosigmoid
Course: Negligible mortality	Course: High mortality if untreated

and Bill[12] in 1948 devised a surgical procedure for the treatment of this condition. The aganglionic segment of bowel was resected after it had been pulled through the anus. Continuity was then re-established between the colon and anus, and anal sphincter function was preserved. This approach gave tremendous impetus to the therapy of neurogenic megacolon, and Swenson[1] has now reported the relief of symptoms in 82 patients by this procedure. Hiatt[13] has had similar successes in a smaller number of patients using his modification of the technic.

Since the intestine cannot function normally in neurogenic megacolon without surgical excision of the aganglionic segment and since in psychogenic megacolon the bowel is capable of functioning physiologically without surgery, differentiation of the two diseases is of utmost importance. The historical and clinical features which are most helpful in this distinction are summarized in table 2.

Patients with neurogenic megacolon have constipation but not fecal soiling as the major complaint. Additional characteristics which are useful clinically in establishing the diagnosis are as follows: onset at birth or in the first few weeks of life, use of the toilet for defecation, attempted defecation in the sitting position, pellet-like or ribbon-like stools, frequent episodes of intestinal obstruction, an empty rectum, presence of a spastic segment of rectum or rectosigmoid using Neuhauser's fluoroscopic technic[5] and eventual death if untreated.

Anatomic Megacolon: A third group of patients has been recognized for many years in which megacolon is due to organic, obstructive lesions. Lee and Bebb[4] state that the commonest cause of this condition in the pediatric age group is stricture formation following surgery for an imperforate anus. Congenital anorectal stenosis is a less frequent cause. Rarely symptoms are produced in children by extrinsic or intrinsic tumors which obstruct the fecal stream in the distal colon. The diagnosis of these cases can usually be made by digital examination of the rectum. The authors employ the term anatomic megacolon for this group.

Classification of Megacolon: With the recognition of the psychogenic group it is felt that all cases of megacolon can now be differentiated and classified. Such a classification will promote accuracy in the differential diagnosis of the symptom of megacolon and prevent ill-advised or harmful surgery in patients who cannot possibly be benefited. Only the neurogenic and anatomic groups may be expected to improve as a result of surgery. The authors have found the following classification to be useful:

I. Psychogenic megacolon
II. Neurogenic megacolon (aganglionic segment of bowel)
III. Anatomic megacolon
    Stricture following surgery for imperforate anus
    Anorectal stenosis
    Intrinsic or extrinsic obstructing tumors

Summary

The results of surgical therapy in cases of aganglionic megacolon have tended to create the impression that all cases of megacolon can be benefited by surgery. The authors have described six patients in whom megacolon had a psychogenic origin; this group has been previously described as "functional" or "idiopathic," and its psychogenic origin has not been clearly recognized. Psychogenic megacolon may be diagnosed by the following

clinical findings without the necessity of a detailed psychiatric history: admitting complaint of fecal soiling, onset in the second year of life or later, infrequent use of the toilet for defecation, defecation in the standing or supine position, inhibition of the stool, periodic voluminous stools, absence of episodes of intestinal obstruction, a feces-packed rectum, absence of a spastic segment of rectum or rectosigmoid using Neuhauser's fluoroscopic technic[5] and a relatively benign course insofar as physical status is concerned.

A sharp clinical distinction is apparent when the following findings of the aganglionic group are considered: admitting complaint of constipation without fecal soiling, onset at birth or in the first few weeks of life, use of the toilet for defecation, defecation in the sitting position, pellet-like or ribbon-like stools, frequent episodes of intestinal obstruction, an empty rectum, and the presence of a spastic segment of rectum or rectosigmoid using Neuhauser's fluoroscopic technic.[5]

A small additional group of cases has been described by others in which megacolon is due to anatomic obstruction; these cases can usually be diagnosed by digital examination of the rectum.

The authors have classified the symptom of megacolon into three groups and have given them the following generic designations: psychogenic, neurogenic and anatomic. Only the neurogenic and anatomic groups are benefited by surgery.

References

1. Swenson, O., Congenital megacolon (Hirschsprung's disease), Pediatrics **8**:542, 1951.
2. Bodian, M., Stephens, F. D., and Ward, B. C. H., Hirschsprung's disease and idiopathic megacolon, Lancet **1**:6, 1949.
3. Lee, C. M., Bebb, K. C., and Brown, J. R., Selective management of megacolon in infants and children, Surg., Gynec. & Obst. **91**:281, 1950.
4. Lee, C. M., and Bebb, K. C., Pathogenesis and clinical management of megacolon with emphasis on fallacy of term "idiopathic," Surgery **30**:1026, 1951.
5. Swenson, O., Neuhauser, E. B. D., and Pickett, L. K., New concepts of congenital megacolon, Pediatrics **4**:201, 1949.
6. Huschka, Mabel, Child's response to coercive bowel training, Psychosomatic Med. **4**:301, 1942.
7. Tiffin, M. E., Chandler, L. R., and Faber, H. K., Localized absence of myenteric plexus in congenital megacolon, Am. J. Dis. Child. **59**:1071, 1940.
8. Whitehouse, F. R., and Kernohan, J. W., Myenteric plexus in congenital megacolon, Arch. Int Med. **82**:75, 1948.
9. Zuelzer, W. W., and Wilson, J. L., Functional intestinal obstruction on congenital neurogenic basis in infancy, Am. J. Dis. Child. **75**:40, 1948.
10. Hiatt, R. B., Pathologic physiology of congenital megacolon, Ann. Surg. **133**:313, 1951.
11. Swenson, O., Rheinlander, H. F., and Diamond, I., Hirschsprung's disease: New concept of etiology, New England J. Med. **241**:55, 1949.
12. Swenson, O., and Bill, A. H., Resection of rectum and rectosigmoid with preservation of sphincter for benign spastic lesions producing megacolon, Surgery **24**:212, 1948.
13. Hiatt, R. B., Surgical treatment of congenital megacolon, Ann. Surg. **133**:321, 1951.

Spanish Abstract

Megacolon Psicogénico Manifestado por Encopresis

Los autores analizan 6 casos de megacolon en los cuales excluyeron la existencia de un segmento intestinal con ausencia de ganglios, basándose en la historia clínica, la exploración física, y la fluoroscopía con la técnica de Neuhauser. Ilustran el padecimiento con el caso clínico siguiente: Se trató de un niño de 11 años de edad que fué internado al hospital por encopresis. Fué niño a término que tuvo ictericia de causa desconocida durante el período neonatal. A las 3 ó 4 semanas de vida tuvo

evacuaciones con rasgos de sangre, poco frecuentes, pero acompanadas de dolor sugiriendo la presencia de fisuras anales. Se alimentó a la botella, pero raramente era cargado por la madre para alimentarlo. Al iniciarlo en su adiestramiento para controlar sus evacuaciones, cuando tenía un año de edad, se le colocaba en una silla especial, pero raras veces se tuvo éxito y defecaba generalmente en los pañales. Pronto la madre comenzó a darle de nalgadas aunque sin éxito, entonces principió a mimarlo, a rogarle y aún a ofrecerle premios logrando como resultado que el niño se sentara en la borcelana y pujara, pero continuaba haciendo sus evacuaciones en su ropa. Al final del segundo año de edad se le aconsejó a la madre usar laxante y enemas como medio para adiestrarlo pero se defendía gritanto, pateando y apretando el esfinter anal. Ya casi de 3 años se le ordenaba que fuera a defecar pero mentía diciendo que lo había hecho y mas tarde lo hacia en sus ropas y mientras al segundo año no tenía enuresis ni diurna ni nocturna, nunca se logró el control de sus evacuaciones.

El enfermo era hijo ilegítimo, nació cuando su madre tenía 19 años y causó gran resentimiento de parte del abuelo del niño. Vivió con los abuelos durante los primeros siete años y estos tuvieron que atenderlo en gran parte. Entonces murió el abuelo y la madre que se había casado un año antes lo recogió, pero la encopresis continuó siendo motivo de disgusto constante entre ésta y el padrastro. La madre lo obligaba a llevar una almohadilla que le metía en sus pantalones y así lo mandaba a la escuela lo cual motivó que se escapara de la casa en varias ocasiones, siendo golpeado rudamente por su padrastro. Tres meses antes de internarse en el hospital había huído de su casa y vivía con una familia con quien hizo amistad y fué quien lo llevó al hospital.

La madre del niño era una persona apática, desnutrida, y débil físicamente desde su infancia, parecía ser, tanto física como emocionalmente, un ser inadecuado para llenar su papel materno y el enfermo la consideraba mas como hermana que como madre. Deseaba llevárselo a su casa pero no había hecho intento alguno previo a la hospitalización del enfermo y trataba de congraciarlo ofreciéndole que dejaría a su esposo si volvía con ella.

La exploración demostró un niño desnutrido, pequeño, de apariencia inmadura y sin caracteres puberales. En el lado izquierdo del abdomen se palpaban grandes masas fecales; no había lesión obstructiva rectal al tacto digital, el esfinter anal tenía tono normal y el recto estaba lleno de escíbalas impactadas. A la fluoroscopia con la técnica de Neuhauser no se encontro segmento espástico del aza rectosigmoidea pero con enema baritado se demostró un megacolon que se iniciaba desde el ano. Durante 3 meses de observación en el hospital, no se vió mejoría alguna, continuó evacuando estando de pie o acostado en la cama, nunca en el baño, ocasionalmente tenía cólicos. No le perturbaba el olor fecal que despedía. Su conducta era inmadura, siempre fué obediente y conforme, no parecía tener interés en las cosas sexuales y nunca se masturbó. No demostraba emoción o sentimiento alguno al hablar de sus síntomas o de su situación familiar.

Las características mas importantes de los 6 enfermos estudiados por los autores y que permiten hacer el diagnóstico del padecimiento fueron las siguientes: A. Encopresis.—Se presentó como síntoma principal preadmisión hospitalaria en 5 de ellos, en el 6° se desarrollo mas tarde. Todos los métodos para deternerla fracasaron y solo se vieron mejorías temporales por los enemas o grandes defecaciones espontáneas. El olor fecal era inadvertido por los enfermos. B. Principio.—Entre los 3 y 9 años, es decir, después de que el desarrollo neuromuscular generalmente permite el control voluntario del esfinter anal externo sugiriendo que la inhibición de la defecación es un factor importante. C. Adiestramiento coercitivo del control anal.—En 4 enfermos fué indudable: enemas, adiestramiento precoz, castigos, congraciamiento marcado etc. D. Hábito de defecación en el baño. —Tres de los enfermos nunca lograron controlar su esfinter anal; en los otros 3 si lo hubo y en edad usual pero desapareció después un período variable de 1 hasta de 6½ años de rutina normal, sin embargo, continuaron orinando en el baño. E. Defecación en posición de pie o acostado.— Aun cuando esta posición hace suponer normalmente que no facilita la defecación sino que la inhibe, concomitantemente con el principio de la encopresis se inició en los enfermos este hábito de defecación. Cuatro de los enfermos cuando defecaban se escondían, en rojecían de la cara y permanecían de pie con las piernas apretadas una contra otra. Frecuentemente también lo hacían ya en la cama. F. Cólicos abdominales.—Se presentó en 3 enfermos, ninguno tuvo vómitos, ni cuadros sugestivos de obstrucción intestinal. Se interpretaron como la inhibición voluntaria del enfermo para evitar la defecación pero ineficientemente quizas, pues no lo lograban. G. Palpación abdominal de masas fecales.—En épocas distintas se encontraron en todos los casos variando en cantidad de acuerdo con la frecuencia y volumen de las evacuaciones. H. Escíbalas impactadas en el recto que era corto. I. Ausencia de un segmento espástico del recto o aza sigmoidea. J. Observaciones psicopatológicas.

—La mayoría de los enfermos eran sorprendentemente obedientes y conformes, limpios excepto de su encopresis, buenos escolares, frecuentemente favoritos de los profesores, causaban impresión favorable en los adultos, controlaban todos sus actos hostiles y agresivos, o sus emociones exageradas y frecuentemente tenían actitudes estóicas. Las madres de los enfermos eran incapaces de expresar sentimientos genuinos y la única atención que brindaron a los enfermos fué fundamentalmente en relación con los cambios de los pañales. K. Evolución.—Las condiciones de los enfermos fueron excelentes durante todo el tiempo y en 3 de los casos en que sus medidas estaban en los porcentilos inferiores se atribuyó el hecho a trastornos nutritivos asociados. En los 5 casos no descritos la enfermedad variaba de 6 meses a 4 años. Bodian reporta que no hubo muertes en 34 casos similares así que el padecimiento es benigno contrastando con la alta mortalidad en megacolon aganglionico.

Los autores afirman que en la actualidad todos los casos de megacolon pueden clasificarse dentro de los tres tipos siguientes. I. Megacolon Psicogénico. II. Megacolon Neurogénico. y III. Megacolon Anatómico: estenosis postoperatoria por ano imperforado, estenosis anorectal y obstrucción tumoral intrínsica o extrínsica, siendo el diagnóstico diferencial factible. Solo se benefician con terapeútica quirúrgica adecuada los dos últimos tipos de megacolon.

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SHORT TERM MANAGEMENT OF A CHILD BEHAVIOR DISORDER

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THE treatment of childhood behavior disorders is often a complex problem not only in understanding the tensions within a family group but also in dealing with the physician-parent relationship in such a way that the insights available to the physician can be made useful to the parents in terms of a positive program of help for the child. The following case report of a severe behavior disturbance in a four year old boy with a brief therapy involving the patient's parents, the pediatrician and the psychiatrist resulting in a rapid reversal in what had appeared to portend a stubborn and difficult long term problem is reported to examine the factors which made this result possible.

CASE REPORT

Patient was first seen at age of 3 yr., 9 mo. Mother complained of these difficulties: 1. Since toilet training began at the age of about 16 mo., child persistently refused to sit on toilet or to give up use of diaper. He screamed with fear and insisted on having bowel movement in a diaper. When he become old enough to verbalize, he would say that he could not stand the smell. Later, he also demanded that rubber pants be kept on over the diaper for fear that "B.M." would "fall out." Thus at age of 4 yr. it was necessary to keep child day and night in a diaper and rubber pants. 2. He refused to stay in his own bed at night but crawled into mother's bed. On some occasions he aggressively demanded that she stay in his room with him or he would not go to sleep. 3. The mother had never been able to get the child to give up his night bottle before falling asleep, although he would drink milk from a glass at daytime meals. 4. He was subject to fits of temper in which he hit and destroyed objects. Mother also related that these traits were largely in relation to herself and to a lesser extent to the father and the maternal grandmother. He had consented on occasion to use the toilet at the maid's request.

Patient is an only child. Both parents are school teachers of superior intellectual attainments. They were married rather late in life and remained childless for about 7 yr. by intention. Rationalization for this was need for economic security before having a child. Patient was breast-fed for 1st 9 mo. Solid foods were begun at 3 mo. and were taken well. Weight gain was normal. He sat up at 6 mo., walked at 10½ mo. and talked at 26 mo. When he was 18 mo. old, mother returned to work, again for economic reasons. He was left in the care of a maid with supervision by maternal grandmother. Toilet training difficulties seem to have been roughly coincident with mother's resumption of teaching.

When patient was first examined by the pediatrician, he came reluctantly from waiting room into office. Once in office he began aggressively to brush things off the desk. He then picked up various objects and threw them at the wall or in the general direction of the physician. He said "I hate you—I want you to go away." He ran wildly around office and examining room kicking at bookcases, walls and tables and violently slamming doors. When little attention was paid to him, he finally became calm and submitted to physical examination exclaiming an occasional "no" and "I don't want to."

Physical examination was negative except for a small right inguinal hernia.

At this initial contact some of the child's resentments were explained to the mother and nursery school was recommended. Parents were advised to handle him more firmly and consistently but because of seeming magnitude of the problem and intensity of mother's guilt feelings the case was referred to the group psychiatrist for guidance of both mother and pediatrician.

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In the first psychiatric interview with the mother it was immediately apparent that she was an ambivalent parent who was in great conflict over her desire to earn a living in her profession and her role as a mother. Her reaction to this conflict was to continue her job in which she functioned well but to masochistically blame herself for all the child's difficulties. From the first day of her return to work she had made it almost a daily practice to bring the child small gifts as a kind of "peace offering." Father also indulged in this behavior. She remarked on this first occasion, "It is probably quite simple, I know that it is all my fault, I am sure that all you can do is to tell me to give up my job and stay home with my child until he gives up his baby habits." She was looking for criticism and punishment from the psychiatrist and yet it was quite obvious that such advice would have been rejected. Instead it was carefully pointed out to her that the removal of a mother from her child, even at 18 mo. does not invariably produce behavior problems particularly when a reasonably competent substitute is available. However, it was stated, the mother's own attitude (toward her absence from the child) may be such a guilty one that it makes it impossible for her to deprive the child of those things that he would ordinarily give up to please her. It was suggested that a feeling can be transmitted to the child that the mother must be "bad" because she leaves him and that therefore he is entitled to demand restitution from her in the form of indulgent treatment.

This formulation seemed to impress the mother. Knowing something of educational theory and common sense child rearing, she was ready for the insight that took the onus of responsibility from her work and placed it upon her sense of guilt. Later, in recalling the conversation, the mother said, "I was so relieved that it was not me but my guilt feelings that I got the courage to go ahead and do what I had to do in the first place." The program of action agreed upon was first to remove rubber pants and diaper. Patient was then to be left to his own devices as to whether he would defecate in what, to him, would have been a highly unaesthetic and exposed manner, or to use the toilet as a lesser evil. As had been predicted, his first maneuver was to test his mother's new and incredible resolve by a complete bowel retention which lasted for several days. This was terminated by the use of a mild cathartic and gentle but firm encouragement to use the bathroom. After violent but now vain outcries for diaper and rubber pants, the battle was finally won and within a week he was beginning to announce proudly that "it was fun to use a toilet." At this point another problem arose. Mother was so impressed with her new found ability to produce change by deprivation, that she called to say that she was about to take away the night bottle and deny the usual request that she sleep in the child's room at night. It was apparent that success was producing an enemy whose approach would come from the opposite direction and that in her enthusiasm the mother would deprive the patient of all his infantile gratifications at once. This burden on his adaptive capacity could well scuttle all that had been accomplished. This was explained under the slogan of "solving one problem at a time." It was agreed that future deprivations would not be undertaken until the current problem had been stabilized.

At first the toilet routine involved the mother's remaining with him during defecation. A short time later he was willing to compromise on the father as a suitable substitute. About 12 wk. after institution of the new program, he seemed disposed to answering his own defecatory impulse.

The father is an indulgent and "tolerant" individual with many years of experience in the field of education. He is described as intellectual, energetic in his own work in activities outside of home but passive and "given to just sitting himself in one place and letting the women folk take care of things" while at home. His general attitude toward the patient's difficulty was: "If everyone just keeps his head and doesn't get excited" and if there is a minimum of coercion, "then things will just work themselves out in the long run." This attitude expressed his problem *vis-à-vis* both the child and his wife. Toward the child he also felt guilty for condoning the mother's "defection" and by many small gestures indicated his need to make some atonement. He tended to discourage his wife in her abortive attempts to deprive the patient of infantile gratifications. This often took the form of siding with the child when a conflict arose between child and mother. In the face of this combination of forces, the mother's resolution always vanished. One of the obvious results of the mother's contact with both the pediatrician and the psychiatrist was to give her a sense of having the "stronger battalions" on her side. Following her interview with the psychiatrist, the father stopped intervening when the child protested.

Theoretic Considerations

The toilet problem was chosen from among the complaints as the main focus of attack

for the following considerations: First, the child was getting close to school age. Of all his infantile traits the one connected with wearing rubber pants and the inability to attend to his own toilet needs would constitute the greatest barrier to any kind of satisfactory school adjustment. Second, it is known from the data of child-development studies that there is an important relationship between the period of achieving anal sphincter control and future personality traits. When the child was 16 months old the mother had gone to work and had set a major problem in readjustment in addition to the emotional problems of toilet training. This was made even more acute by her own reactions of guilt and atonement to the child as described above. This aspect of the problem was further borne out not only by the behavior symptoms connected with the toilet but by certain emergent traits which clinical psychologic investigation has shown to be intimately connected with the resolution of the problems faced during the period of development of anal sphincter control. The most striking of these was the consistent way in which the patient managed to extract something from his parents as a precondition of giving up anything belonging to him. Although this is not an unusual characteristic, it had an exaggerated quality in this patient. Thus when he was urged to sleep in another room in the house, he objected violently but finally consented on the condition that he be given the room then occupied by the grandmother while she would be dispossessed to other quarters, in spite of the fact that the room chosen for him was in all other ways more attractive. This was also seen in the method of his fighting retreat from the need to defecate at will in a diaper. At first, a complete retention of bowel contents followed by a compromise, to the effect, "I will give up the bowel contents if in return my parents read to me while I sit in the bathroom" (a concession made in return for the one he feels forced to yield). This always went further than the requirement of a mere token concession. The "return" consideration on the part of the parents always had to have the trademark of an annoying deprivation for them. Thus they must come to read him a story only when they were most likely to feel this as an imposition, e.g., while eating their supper or getting ready to leave the house for work. Other characteristic traits of this period of development were his stubbornness, his tendency to show his antagonistic feelings by a free use of fists and thrown missiles and the quick and violent reversal of his feelings between demonstrations of hatred and affection and between rebellion and submission.

The reversal of the behavior symptoms is not the only long term objective. In addition, the development of certain character traits, as described above, can be prevented by early reversal of the bowel symptoms. It must be confessed, however, that treated in this "counselling" fashion, such an outcome is less predictable than with more precise psychotherapy.

The Doctor-Parent Relationship

It is felt that the outcome in this case could only have been possible in such a short time with a certain fortuitous concatenation of circumstances. First of these was probably the receptivity of the parents, particularly the mother, to outside help. Second, was the sympathetic and noncritical relationship between the mother and the pediatrician. Third, was the ready availability, to the pediatrician, of psychiatric counselling, as well as the possibility of constant exchange of ideas between psychiatrist and pediatrician, with a mutual interest on the part of both in the data that each was able to gather through his own particular orientation. The authors also feel that a psychodynamic orientation frequently makes a quick panoramic impression of the problem possible, that would require a greater

period of time with another frame of reference. Thus, in a situation that allows very little time for psychiatric investigation, one finds understanding based upon modern concepts of child growth and development to be of inestimable value.

Treatment Through the Parent

There is considerable precedent, not only for counselling of children's neurotic problems with the therapy to be carried out by the parent, but even for the psychoanalytic treatment of children by the parent. The first child analysis was carried out by Freud[1] in this fashion in a case of childhood phobia, through interviews with the father. Reuben[2] reports on the treatment, through counselling of the mother, of two children who were sisters. Rangell[3] in a most interesting running account discusses the treatment of nightmares in a seven year old boy by letter correspondence with the father three thousand miles away. Kubie[4] and Grotjahn[5] have also dealt with this problem.

There are many drawbacks as well as the obvious advantages to such attempts at child psychotherapy. It is limited to parents who have a certain degree of sensitivity and "psychological awareness" to their own conflicts as well as the childs. It necessitates a special kind of *rapport* between the parent and advising physician and it is only possible where the parent is not too deeply involved in the neurosis of the child nor made too anxious by the program that must be carried out. Where these conditions are not met such efforts are likely at best to be waste motion and at worst deleterious.

Summary

A seemingly obstinate case of refusal to be toilet trained in a four year old boy was treated by brief counselling of the mother. The interpretation of her own conflict was the major factor in the reversal of the child's problem. The rather striking results are discussed in terms of the parent-pediatrician relationship and the pediatrician-psychiatrist team work. The effect of bringing a psychodynamic point of view to bear in the elucidation of intrafamilial tensions is evaluated.

References

1. Freud, S., Collected Papers, London, Hogarth Press, 1933, vol. 3.
2. Reuben, M., in Psychoanalytical Study of the Child, New York, International Universities Press, 1945, vol. 1, p. 247.
3. Rangell, L., in Psychoanalytical Study of the Child, New York, International Universities Press, 1950, vol. 5, p. 358.
4. Kubie, L. S., Resolution of traffic phobia in conversations between father and son, Psychoanalyt. Quart. 6:223, 1937.
5. Grotjahn, M., Relation of child analysis to education, Bull. Menninger Clin. 1:184, 1937.

Spanish Abstract

Manejo en Corto Plazo del Trastorno de Conducta de un Niño

El tratamiento de los desórdenes de conducta del niño es un problema complejo que exige no solo entender las tensiones que privan dentro del medio familiar sino obtener una relación médico-paternal de tal naturaleza que los factores que el pediatra descubra pueda hacerlos de utilidad para los padres integrando un programa de positiva ayuda para el niño.

Este caso ilustra un trastorno severo de la conducta tratado en colaboración con los padres, el pediatra y el psiquiatra que produjo el éxito en corto tiempo de lo que parecía ser un problema difícil, persistente y de larga duración.

El niño tenía tres años nueve meses cuando fué visto por el pediatra porque desde los 16 meses de edad, al tratar de iniciarlo en sus hábitos normales de defecación en el baño se resistía indefectiblemente y no quería abandonar la costumbre de hacerlo en el pañal, argumentando que no podía soportar el olor, cuando ya fué capaz de expresarse y exigía que lo tuvieran continuamente con calzones de hule sobre el pañal por temor de que el excremento se le "cayera fuera" y así lo hicieron los padres. Además, se rehusaba a permanecer en su cama durante la noche y se subía a la de su madre amenazando de que no se dormiría si no se estaba con él en su cuarto. También no había sido posible romper el hábito de quedarse dormido en la noche tomando la última botella de leche aunque ya estaba acostumbrado a tomarla directamente del vaso durante el día, y por último, presentaba ataques de coraje durante los cuales golpeaba y rompía cosas. En su gran parte, estas manifestaciones eran en relación con la madre y menos con el padre y la abuela. Era niño único, de padres de nivel intelectual superior, profesores, y nació 7 años después de su casamiento por desear tener seguridad económica previamente. Su desarrollo físico y mental fué normal. Cuando tenía 18 meses, la madre, con el consentimiento paterno, volvió a trabajar y el niño se quedó a cuidado de una sirvienta supervisada por la abuela. En la primera consulta el niño entró al consultorio sin desearlo y ya adentro tiró los objetos del escritorio del pediatra y los tiraba contra la pared o hacia donde estaba el médico y le dijo: "Te odio, quiero que te vayas." En seguida, corría alocadamente pateando los libreros, paredes y mesas y cerraba las puertas golpeándolas. Finalmente, cuando casi no se le prestó atención, se calmó y sometió a la exploración física exclamando ocasionalmente "no" y "no quiero." Solo una pequeña hernia inguinal derecha se le encontró.

Se explicó a la madre algunos de los resentimientos del niño y se aconsejó mandarlo al "jardín de niños," tratarlo con mas firmeza y persistentemente y se pidió entrevista con el psiquiatra. Esta hizo aparente que la madre estaba en gran conflicto entre su deseo de ganarse la vida en su profesión y su papel de madre, deseaba continuar su trabajo declarándose culpable de todas las dificultades del niño y desde el primer día en que volvió al trabajo regresó a casa con un regalito para el niño para "hacer la paz," con la indulgencia del padre. En esta entrevista la madre comentó la solución así: "Probablemente es bastante sencillo, se que es toda mi culpa, y es seguro que todo lo que usted puede hacer es decirme que abandone mi trabajo y me quede en casa con mi niño hasta que él abandone sus hábitos infantiles." Buscaba que el psiquiatra la criticara y castigara pero era obvio que dicho consejo sería rechazado. En lugar de esto se le indicó cuidadosamente que la ausencia materna, aun a tal edad, no producía invariablemente problemas de conducta sobre todo cuando se le substituye competentemente, sin embargo, que la actitud de la madre podría ser de tal sentimiento de culpabilidad que la hiciera incapaz de privar a su hijo de aquellas cosas que generalmente el abandona por propia voluntad para agradarla. Se le sugirió que el sentimiento de que la madre debe ser "mala" porque deja al niño puede trasmitírsele a éste y por consiguiente que es lo debido demandar compensación bajo la forma de tratamiento indulgente. Esto impresionó a la madre profundamente pues le dió valor para proceder sabiendo que no era ella misma sino sus sentimientos de culpabilidad los responsables de la situación. El programa ma de acción fué primeramente dejarlo sin calzones de hule y sin pañal. Como fué previsto, el niño puso a prueba esta decisión de la madre provocando una retención intestinal completa varios días que terminó con la administración de un purgante ligero y entusiasmándole, al mismo tiempo que insistiendo con firmeza, a usar el baño. Finalmente, no sin llantos violentos pero en vanos, se ganó la batalla y a la semana ya el niño anunciaba orgulloso que "era divertido usar el baño." Con este éxito la madre pronto decidió suspender la botella de la noche y negarse a dormir en el cuarto del niño, con el peligro de que fuera demasiado exigirle a su capacidad de adaptación y perderse todo lo que se había logrado. Se acordó que las privaciones futuras no se iniciarían hasta que el problema actual no estuviera estabilizado. En un principio el niño exigía la presencia de la madre mientras defecaba, después accedió que fuera substituída por el padre, y a las 12 semanas era capaz de hacerlo por sí mismo aun cuando la familia estaba lista a ayudarlo si lo pedía.

La participación del padre en la génesis del problema fué la de elemento pasivo, indulgente, en ocasiones tomando el lado del niño, y esperando que el tiempo diera la solución, pero después de aceptado el programa del psiquiatra no intervino mas cuando el niño protestaba.

Se escogió como centro principal de ataque el problema de la defecación del niño entre los múltiples que tenía porque se acercaba a la edad escolar y éste ofrecería una gran barrera a su adaptación en la escuela y porque es sabido que existe una relación importante entre el periodo en que se logra el control del esfínter anal y las características futuras de la personalidad y así se interpretaron las manifestaciones de conducta durante el tratamiento en que insistía persistentemente en obtener

algo de los padres como condición previa a abandonar lo que le pertenecía: cuando se le urgió que durmiera en otro cuarto, lo objectó violentamente pero al final consintió con la condición de que se le diera el de la abuela aunque el ofrecido era mas atractivo; para dejar de retener las evacuaciones al principio exigió que sus padres le leyeran algo mientras estaba defecando y mas aún, lo planeaba cuando obviamente significaba una imposición para los mismos, por ejemplo, mientras comían o estaban a punto de salir al trabajo. Otros rasgos característicos de este periódo de desarrollo eran su tendencia a mostrar sus sentimientos antagonistas cuando golpeaba o tiraba las cosas y su rápida y violenta inversión de sus sentimientos entre demostraciones de odio y afecto y rebeldía y sumisión. Con la desaparición temprana de las manifestaciones de la defecación se espera que se prevengan el desarrollo de otros rasgos de su caracter, como los descritos arriba, aunque tratadoen esta forma es mas difícil predecirlo que si se usara una psicoterapia precisa.

La receptividad de los padres, particularmente de la madre, a la ayuda brindada, las relaciones de simpatía entre la madre y el pediatra, la consulta del psiquiátra a la mano, y el constante intercambio de ideas entre uno y el otro con sus propias orientaciones decidieron el final del caso rápidamente.

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AMERICAN ACADEMY OF PEDIATRICS, INC. PROCEEDINGS AND REPORTS

Round Table Discussion

ETIOLOGY, RECOGNITION, PREVENTION AND TREATMENT OF RHEUMATIC FEVER

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LEON DEVEL, M.D., Grand Rapids, Mich., and WILLIAM C. VANCE, M.D., Richmond, Ind., *Secretaries*

Chairman Gibson: For a good many years, it seems to me, we have been hashing over the same old problems of rheumatic fever without making much progress in our knowledge of the disease. Recently, however, I think there are hopeful signs that we are learning a little bit more about rheumatic fever and will be a little better able to deal with it.

As you all know, rheumatic fever is a disease with many varied manifestations. Some cases are so outright that even a junior medical student could make a diagnosis; other cases are so obscure that at a given time and in a given case one is quite unable to make a definite diagnosis. Yet within a wide scope of variations it seems to me that rheumatic fever does show a definite group of phenomena which, by careful study, one can usually evaluate in the course of time and thereby determine whether rheumatic fever is present.

I felt we might best handle the subject by dividing our discussion on rheumatic fever into 4 parts: etiology, recognition, prevention and treatment. At this time I want to introduce to you Dr. Edward C. Lambert, who is my associate in this Round Table discussion. He is at the University of Buffalo Medical School in Pediatrics and in charge of the Cardiac Children's Clinic.

Dr. Edward C. Lambert, Buffalo: About 50 years ago Dr. Osler defined rheumatic fever as an acute noncontagious febrile infection depending on an unknown infectious agent, characterized by multiple arthritis and a special tendency to involve the heart. It is still true that we don't know the cause of rheumatic fever, but the research carried on in the past 50 years has brought results that should not be forgotten. It is now widely accepted—not completely but very widely accepted—that most if not all attacks of rheumatic fever are precipitated by group A streptococcal infections. There is a large body of evidence, both from the epidemiologic studies and from the immunologic studies. In addition the apparent ease with which it is possible to prevent recurrent attacks of rheumatic fever using chemotherapy or antibiotics offers further evidence.

The epidemiologic evidence is familiar to all of you. One of the main points to be mentioned is the statement that it was proved during the last war that there has never been an epidemic of rheu-

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matic fever without a preceding epidemic of streptococcic infection. The association of both streptococcic infections and rheumatic fever as regards environmental factors that are so often discussed—dampness, seasonal change, climate—is a rough parallel between the 2 which doesn't often offer proof in any sense, but which is evidence.

The drop in mortality and morbidity in both rheumatic fever and the streptococcic infections, the fact that we don't see children dying with scarlet fever any more, is suggestive. The immunologic evidence is, of course, the fact that we can find by the presence of antibodies, specific antibodies to the group A streptococci in the blood of such a high percentage, 80 to 90% and maybe 100%, of children with rheumatic fever, which merely indicates in them that there was a preceding streptococcic infection. We still don't know the mechanism and the allergic concept is the one that has the highest favor and the best evidence at the present time. There is no proof but the most convincing evidence comes from the man working on the possibility of an allergic mechanism.

The details of these evidences should come out in the discussion because many of them are too familiar to all of us for me to go into them now.

The possibility of [direct toxic] injury is still wide open for proof and may be an entire answer. The original belief that other organisms may cause rheumatic fever has been almost discarded, but it was still being discussed as a possibility at the last meeting of the Heart Association. There is no confirmed evidence that it is caused directly by a virus or associated form of bacteria. The other factors of heredity and age can be discussed later on.

New Speaker: I think you must accept chorea which is associated with rheumatic fever.

Dr. Lambert: It is apparently well established now that the antibodies do not appear in the blood stream in chorea in anywhere the frequency they appear in rheumatic fever. Some proponents who think it is streptococcal argue that it might be the failure of brain tissue to produce those antibodies.

Dr. James P. Conway, Milwaukee: It has always been my belief that there is an emotional factor in the etiology of rheumatic fever. I base that on some of the work of Dr. T. Duckett Jones during the war: the men were definitely emotionally upset as well as exposed to streptococcal infection.

Dr. Saul J. Robinson, San Francisco: Is it the infection alone that acts as the trigger mechanism?

Dr. Lambert: There is no confirmed or accepted evidence of anything else.

I think now we should discuss the hereditary factor to some extent. May Wilson and her coworkers have amassed and analyzed a tremendous body of data which indicates, at least to them, that it is caused by a single recessive gene. A lot of people have accepted this but there are still a good many men and a good many papers appearing that disagree at least to the extent of its being a predisposition on the basis of a single recessive gene. They feel that common environmental factors play a great part while obviously there is a marked individual susceptibility.

There is also the possibility that a number of men feel strongly, although without any good evidence, that rheumatic fever may be as widespread as polio. But the clinical manifestations may only appear in a small percentage of the population. There again there is certainly going to be the factor of individual susceptibility. The evidence for that is suggestive again. There are a number of reports, one of which shows microscopic stigmata of rheumatic fever heart disease in as high as 90% of normal findings. This was on routine autopsy findings and on people who were not thought to have heart disease. Of course, you get down to whether the pathologist really knows and they do argue among themselves. There is obviously hereditary predisposition but whether it is a single recessive gene, I think, still remains to be proved.

Dr. F. H. Fehlmann, San Diego: I would like to ask Dr. Lambert to elaborate on the statement he made in regard to declining mortality in scarlet and other streptococcic infections and rheumatic fever. Is it possible that we are getting a breed of rheumatic fever that is so subclinical that it is hard to diagnose?

Dr. Lambert: I think that it is quite possible. The feeling is that the antibiotics have caused the decrease in mortality and morbidity. But Dr. George M. Wheatley, for whom I have the highest respect, says that trend was apparent and definite before sulfa. A number of bacteriologists feel strongly, I know, that the streptococcus is changing. We mentioned finding rheumatic stigmata in a large percentage of hearts. Very often after streptococcic epidemics there are a lot of people who are not known to have rheumatic fever but who demonstrate many of the minor manifestations such as minor ECG changes, a prolonged sedimentation rate and vague aches and pains. If I am not wrong, most of the men working in the field feel that these are subclinical cases.

Dr. Carolyn M. McCue, Richmond, Va.: The evidence of allergy—would you discuss this further?

Dr. Lambert: The evidence is the clinical suggestion due to the similarity to serum sickness. The joint pains, the skin manifestations, fever and the observation that the [Aschoff] body is comparable to the localized inflammatory necrotic lesion you find in the [arthus] phenomena due to the antigen antibody reaction locally in the tissues. The experimental evidence is probably the best right now of anything in rheumatic fever. It has been definitely established for a long time that in small animals injections of foreign protein will give, in a high percentage, lesions in the heart that are extremely similar to those found in rheumatic heart disease. There are a number of pathologists who feel that the lesions are not identical and then, arguing for that allergic theory, they say, well, they aren't humans, they are animals so you wouldn't expect them to be identical. But you read those articles—and the whole progress of this disease is very close to that found in rheumatic carditis. These animals give us horse serum. It fits in with the antibody type of response and at least to me it is one of the easiest ways to think about rheumatic fever at the present time.

Rantz's recent work and also Swift's show that infants and small children gave an increasing antistreptolysin response as they got older. That is, after they had a streptococcic infection there is an increase in antistreptolysin response with age. But that was a rough correlation and with wide variations. On the other hand, taking a small series of children who had repeated streptococcic infections, the responses to the first infections were poor but by the time they had 5 or 6 infections, there was a much higher response; however, this is not proof, merely suggestive evidence.

Dr. Henry W. Moore, Columbia, S.C.: Is there any evidence in the group A streptococcus that certain types of streptococcic infection are more prone to precede an outbreak of rheumatic fever?

Dr. Lambert: The answer is no, but to date, and as far as I know, types 4 and 22 have never been shown to precede rheumatic fever. They have had epidemics of type 4.

Swift has had evidence that it is not due to repeated infection of the same type. It seems to be due to repeated infections of different types of the streptococci. If you have repeated infection of the same type, you may not get rheumatic fever at all.

Dr. Lambert: Part of the trouble is that we don't know what rheumatic fever is, that we can't define its limits. When it is full blown, as Dr. Gibson mentioned, it is easy both clinically and pathologically but the limits are unknown and there is complete disagreement about the overlapping. We should mention here that all these allergic experiments with the injection of foreign protein produce a picture of erythema nodosum—it is the heart which shows the carditis.

There is also convincing evidence from one clinical series with autopsy findings where they found mitral stenosis—one of the few points the rheumatic men can agree on. They found mitral stenosis in a high percentage of autopsies of patients with severe rheumatoid arthritis. That was convincing.

I am told that a great many European authorities feel that it is the same disease. Dr. Gibson feels, he has told me, that it is not, that it is quite separate, and I am inclined to agree. I have never seen a child who had both at the same time as far as I can tell.

Dr. Janet S. Baldwin, New York City: We had one child who did have chorea and rheumatoid arthritis active at the same time. She developed a slight mitral systolic murmur suggestive of mild organic heart disease.

Dr. Lambert: Of course there is the little catch that both of them are fairly common diseases. Rheumatoid isn't as common in children but it is not rare either. You expect some overlap just from the frequency of each one.

Dr. Baldwin: How seriously should one take a positive family history of rheumatic fever in the evaluation of a somewhat ambiguous illness which may look like rheumatic fever?

Chairman Gibson: It should make us more suspicious perhaps but it shouldn't lead us to make a diagnosis of rheumatic fever unless we have the evidence.

We will now pass on to the recognition of rheumatic fever in children which is a headache for all of us. I think it is perhaps the most important part of the subject so far as the pediatrician is concerned. I want to stress first of all one manifestation of rheumatic fever and then we will have some discussion.

We all realize that the involvement of the joints is often the first evidence that we have of the presence of rheumatic fever but all of us are more likely to be careless in interpreting the findings we have in this particular manifestation than in almost any other. So often a child is brought to us who has had some pains, a rapid sedimentation rate, a degree or two of fever—does he have rheumatic fever? I think we can get a tremendous amount of information if we will take a little time to question the parents carefully, as to just exactly the nature of those pains which the child has. First

of all, are they actually joint pains or are they muscle pains? I am not convinced that so-called muscle pains are an integral part of rheumatic fever; perhaps they may complain of that in addition to the joint pain. I want to know whether there is redness or swelling of the joint. In the polyarthritis of rheumatic fever, you may have merely pain and tenderness. Do they always complain of pain in a certain part of the body? Are the pains that they have principally leg pains? Do they have pains in both the arms and legs? You have many mothers tell you over and over again that her child has his pains around the knee or behind the knee—well, has your child ever had any pain in the arm? Most of the time they may say they have not. I think if you get this kind of story that is pretty good evidence against its being rheumatic because rheumatic fever doesn't always spare the arms in the course of numerous attacks.

How long do these attacks last? Sometimes the mother will say about 5 or 10 minutes. I don't believe that rheumatic pain allows a child to escape quite that quickly if he has pain due to actual rheumatic fever. There is another thing that has seemed to me helpful: I never ask the mother a leading question—I say, "What do you do for these pains when the child gets them?" Fifty per cent of the time they will volunteer the information that their rubbing the joints gives relief. Now, in my experience you can't rub a rheumatic joint with any success whatsoever. These children want no manipulation of the joints under any circumstances. It seems to me that if we will give more time and attention to the exact nature of these pains of which these children complain, we will get a lot of evidence and a good deal of the time I think that evidence is negative, that is, so far as our being able to make a diagnosis of actual rheumatic joints are concerned. Rarely do we encounter rheumatic joints pains that are limited to a single joint. They usually spread in the course of a day or 2 from one joint to another in rather rapid succession and even if no treatment is instituted, the pain is likely to subside in one joint and progress and manifest itself in some other joint. I am still old-fashioned enough to think that if aspirin doesn't relieve the joint pain in the course of 24 hours, we have probably made a mistake in diagnosis. I have seen child after child come into our hospital in the afternoon and be placed upon adequate dose—1½ grains per pound for the first 24 hours—and you can just tell that child that the next morning those joint pains will be gone. If the pain continues then we have to be suspicious of whether we have made a correct diagnosis. We know that in the early stages rheumatoid arthritis can closely mimic the pains of rheumatic fever but I don't think these pains respond as rapidly or as completely to the use of salicylates as do the pains that are actually rheumatic pains.

Dr. E. S. Wegner, Lincoln, Neb.: To your list of questions I think you should add—What has the child been doing, playing too hard, etc., and is it fatigue?

Chairman Gibson: Yes, that is important. Often you can get the story from the mother, and often pains that occur during the night are from fatigue. Ill-fitting shoes and many other things will precipitate this pain.

Question: Dr. Gibson, would you comment on the more unusual types of pain, the back of the neck, shoulders, back, etc.

Chairman Gibson: There is no doubt that at times we do have pain in these unusual locations. I don't see any reason why we shouldn't expect that. We see frequently pain in the hips, shoulders, etc. But if these locations, shoulders, back, hip, are the only place we see pain we have to be a little skeptical of rheumatic fever.

Dr. Lambert: We have had 2 cases this summer and about 3 or 4 last summer with stiff necks and backs. They were diagnosed as polio and sat in the ward until someone picked up the murmur—or until the murmur developed really. It was an obvious murmur that developed—not at all atypical, but more like mild mitrals. Then these patients went on in the course of rheumatic fever. I wonder, how common that is? Also, we have had a couple of cases of older children where the pains were in the heels and feet. It developed that those 2 were children who had had previous attacks of rheumatic fever.

Chairman Gibson: We get a few patients in our hospital every year that have gone to the contagious hospital with a diagnosis of polio. I think in the early stages it can be difficult to differentiate.

Dr. Ernest T. Heffer, Brooklyn: We have recently had a case just exactly like that. A boy came in with a stiff neck and to complicate the matter he had a heart rate of 46. At first we did not know whether he had a dislocated neck or was developing a brain tumor. Yet the child went on to have typical rheumatic fever.

Dr. Lambert: I can't remember any case of a child with polio in our cardiac clinic.

Chairman Gibson: I will agree with that as far as my recollection goes but there is no reason why they couldn't have both diseases.

Dr. Baldwin: I can remember 2 patients in our clinic who had previously had rheumatic fever and developed polio without paralysis but I don't remember any child who had previously had polio who subsequently came in as rheumatic.

Chairman Gibson: We will now discuss the manifestations of chorea and my conception of it is that it has a definite beginning. It reaches a height and remains for some time and then completely disappears. If there are no complications the child is apparently in as good health as he was before. There has been some material in the literature lately as to the nonrheumatic nature of chorea. I am going to stick my neck out now and say, as far as my own feeling is concerned, that chorea is a rheumatic manifestation and that the burden of proof is on the person who says that it isn't. I would like to hear some expression of an opinion about this from the cardiologists here.

Question: In chorea do you say that the major manifestation of rheumatic infection can occur without any of the other minor manifestations? Are you going to accept that as chorea of rheumatic origin?

Chairman Gibson: If I see a clearcut case of chorea I would consider that a rheumatic child. I know you don't all agree with me so I would like you to speak up.

Dr. Alexander S. Nadas, Boston: I would like to tell you a little bit about an experience we have had at the Children's Hospital of Boston in the past 2 months with 2 cases of Wilson's disease with very definite choreic manifestations. Nobody suspected the diagnosis until the typical Kayser-Fleischer ring was discovered on the patient's cornea. We have never before seen this disease at our hospital and it certainly looked like real chorea.

Chairman Gibson: I think to some extent it is a matter of definition. I like to think that the emotional disturbance in chorea is just as important a part of the disease as the movements themselves. Of course we know that you can get hysterical movements which persist and simulate chorea but they are repetitive; the movements of chorea are constantly varying. As I say it will be a clearcut case where you have a beginning and an end to the chorea and where you have this emotional instability where the child goes to pieces and cries at the slightest provocation—to my mind, that is chorea and as far as my knowledge goes that is a manifestation of rheumatic fever.

Dr. Katherine Dodge Brownell, New York City: I quite agree that Sydenham's chorea is a rheumatic manifestation. I have sometimes felt, though, that one occasionally saw a repeater chorea, that is, a child who had had many attacks, who appeared to have what we called habit spasms on a choreiform pattern. These movements, indistinguishable from those of true chorea, were brought out by the same type of pressure which in another child might lead to repetitious tic movements. I remember well one such child, in whom there was no doubt as to the rheumatic nature of her previous attacks of chorea, who in a period of family stress, had quite marked and typical, constantly varying choreiform movements in the presence of her mother only. She almost appeared to be able to turn them off and on at will.

Dr. Gibson: A kind of hysterical manifestation?

Dr. Brownell: I think you might call it that, although the movements could not be differentiated clinically from those of chorea and we thought of them as habit movements on a choreiform pattern, in a child very familiar with that pattern because of many previous attacks of genuine rheumatic chorea.

Chairman Gibson: Could you answer off-hand how many of the patients with chorea had other manifestations of rheumatic fever sooner or later?

Dr. Brownell: We analyzed that. Of 33 or 35, 50% started with chorea and developed some other manifestation of rheumatic fever subsequently—that is, over a 10 year period.

Chairman Gibson: I think that T. Duckett Jones and his group found as high as 80% showed evidence, either laboratory or clinical, of rheumatic fever.

Neurologists have something to say in this regard; Dr. Douglas Buchanan believes that there is no such thing as psychogenic chorea; he considers chorea to be rheumatic brain disease. I think that possibly there is an explanation for the failure of the increase in sedimentation rate as has been mentioned. Perhaps brain tissue reacts differently. Dr. Buchanan has done some work upon the microscopic pathology in patients coming to autopsy who have had chorea and has found definite changes in the brain. Until we have more definite evidence my own feeling would be that it is a rheumatic manifestation.

Question: In the case of a child who has had a well established chorea and has had maybe 2 or 3 attacks, is it possible for that child in moments of stress to develop temporary chorea-like movements?

Chairman Gibson: Of course, most of those who have worked in the home, the social workers, for example, will tell you how particularly bad the environment is in most of the cases of chorea—broken homes, quarreling, etc. To me that isn't too impressive; you could go among the "best" homes and find plenty of psychologic stress and yet those children don't develop chorea.

Question: Dr. Gibson, could we ask for a show of hands to see how many here believe that there is such a thing as isolated chorea not associated with rheumatic fever?

Chairman Gibson: All right, how many believe that? . . . About 6 here in the audience have that feeling. There is one other thing that it is hard for me to conceive: if chorea is in most instances evidence of rheumatic brain disease, how, apart from the hysteria where the patient mimics someone else, can you get similar movements on a functional basis? That seems to me difficult to explain.

Question: Dr. Gibson, can you tell us something about the seasonal incidence of rheumatic fever? Do all parts of the country show the increase of chorea in November and March as happens here?

Chairman Gibson: I checked on the incidence of chorea in Chicago some years ago and I will say this: it does not have to the same extent the seasonal variation that the other manifestations of rheumatic fever do have.

Dr. Baldwin: I checked on this because I try to separate the repeated choreas from the initial attacks. I had the idea that it might be that the initial attack of chorea followed the season pattern and that repeated attacks would not but I could not find that even the initial attack depended on season.

Question: How much do you depend on fever to aid diagnosis of rheumatic fever?

Chairman Gibson: Well, we can have rheumatic fever without fever. I think that when you have attacks of joint pains almost inevitably they are accompanied by fever. In chorea, the so-called uncomplicated chorea, we do not expect fever. If we have fewer we go back to the rheumatic infection at the time we had the chorea. I think fever, while it is usually present, is not absolutely necessary.

I would like to pass now to another manifestation of rheumatic fever that is also controversial: that is, the skin manifestation of rheumatic fever. We all talk about erythema marginatum and the various perhaps allergic manifestations that go along with rheumatic fever and I want an expression of opinion from the cardiologists here as to whether there is a skin lesion that is pathognomic of rheumatic fever.

Dr. Baldwin: There are children who have a rash at the same time that they have other rheumatic manifestations. It is perfectly possible that that same child who has had a previous attack may go on and have some blushing or blotching which looks like erythema marginatum but I would hate to put him to bed with this as a sign of active rheumatic infection. I personally would not want to diagnose initial or recurrent rheumatic fever on the basis of erythema marginatum alone.

Dr. Brownell: I think in an old rheumatic patient I would be suspicious if he came out with erythema marginatum, but I don't know whether one can make the diagnosis of rheumatic fever on that basis in a not known rheumatic patient, that is, one with no other sign.

Chairman Gibson: I prefer to use the term erythema annulare because I think it is more descriptive than erythema marginatum. When I ask some of the dermatologists what they mean by erythema marginatum, I don't always get the same answer. The thing that I am talking about is erythema that is not elevated, not above the skin, doesn't itch, doesn't burn. The patient doesn't know that he has it. It is elusive. It comes and goes quickly. Have you ever seen it in anything else than rheumatic fever?

Dr. Baldwin: I have seen one case in a child who was not a proved rheumatic patient.

Chairman Gibson: We admitted to Children's Hospital a child with erythema annulare, a child who wasn't sick, had no fever, normal sedimentation rate, no heart findings, no history of joint pains. The child was only 3 or 3½ years old. We put that child through the paces and were not able to find any other rheumatic manifestations. Unfortunately the child was lost from observation and we didn't have a chance to follow up to see whether sooner or later there would be other manifestations of rheumatic fever. Though it is not regularly seen, it occurs in a small percentage of patients. If it once occurs in a patient, it is apt to occur over and over again for a period of days or even weeks. I have a feeling that we can pretty nearly include that among pathognomonic signs of rheumatic fever.

New Speaker: We had one boy who had classical rheumatic fever and heart disease which had

been followed for 10 years at the beginning; he had this rash for a day or 2, he still has it several times a month although according to all other criteria he has been inactive for at least 5 years.

Chairman Gibson: The cases that I have seen that have had this erythema are mostly in children who are active because they are in the hospital, but in a convalescent home in Chicago I know that the physician who supervises there has seen erythema in children who show no other signs of rheumatic activity and felt that they were completely free from rheumatic activity. I have rarely seen rheumatic erythema in a very sick child. I have only seen one child who had rheumatic erythema and nodules at the same time. I look upon rheumatic nodules as a serious manifestation of rheumatic fever. Practically all of these children have severe heart disease.

Dr. Heffer: All the cases of erythema annulare or marginatum that we have seen have been associated with rheumatic activity and recently with treatment with cortisone. It wasn't until we stepped up the cortisone to a very high dose that the erythema disappeared, even though all our other signs of rheumatic activity had disappeared. Yet the annulare persisted until the large dose of cortisone was given.

Chairman Gibson: Years ago Dr. Hayes and I reported 167 instances of rheumatic nodules which we had seen in our hospital. Every one of them was associated with other signs of rheumatic activity and 163 out of the 167 had recognizable involvement of the heart. So that from a diagnostic standpoint I don't think they are important because they appear late rather than early and I have always felt that if you see that the child has rheumatic nodules you scarcely have to examine his heart. You can be reasonably sure that he has had a rather severe rheumatic fever, has had it for a reasonably long time and has had extensive damage to his heart.

Dr. McCue: We have a child right now 8 years old who has had 4 extensive biopsies showing nodules with granulation of the tissues. They come and go and are painful.

Chairman Gibson: Can the pathologist prove those are rheumatic nodules? I rather doubt that. You say they are painful! In my experience, they are not tender.

Dr. McCue: They are not acutely so.

Dr. Baldwin: We have had a case where the nodules appeared first; this was the first case of this type we had seen. Within 2 weeks this child developed a mild carditis which would or could have been missed if the child had not been under close observation.

Chairman Gibson: In my own experience I have not seen them in advance of other definite rheumatic phenomena. When I have seen them present, it has practically always been in a case of severe prolonged heart disease.

We have discussed polyarthritis, chorea, rheumatic nodules, and the skin manifestations of rheumatic fever. I have done that purposely because I feel that those represent manifestations of rheumatic fever and the most important one is the heart disease itself.

As far as I am personally concerned, and I want to emphasize this, I am not able to make a diagnosis of rheumatic fever at any time in any child unless I have one or more of these manifestations. I am completely convinced that rheumatic fever at the present time is frightfully over-diagnosed. Everybody has become allergic to the presence of rheumatic fever. The general practitioner and sometimes the pediatrician doesn't want to make the mistake of omitting the diagnosis and allowing the child to run around with the possibility of rheumatic fever if he has a little heart murmur or something of the sort. Therefore, he leans over backwards, puts the child to bed for 6 months or a year in cases where he is not justified in making the diagnosis. I think we must cling to those major manifestations as emphasized by Dr. T. Duckett Jones. I think in some clearcut cases one can diagnose rheumatic fever from the joint pains alone. If you have a definite chorea, and we agree that the chorea is rheumatic, you can diagnose from that. You can diagnose rheumatic fever from the nodules and possibly from the skin manifestation. Then comes finally the matter of the involvement of the heart. Does or does not the child have rheumatic fever with heart disease? That is the all important question because if it were not for the cardiac involvement it would be an unimportant disease.

It is rather interesting that the diagnosis of both rheumatic fever and rheumatic heart disease is in the hands of the clinician. You have to make the diagnosis on the basis of your experience and your knowledge of rheumatic fever. No laboratory test is going to tell you whether the child has rheumatic fever. In the matter of cardiac involvement of rheumatic fever, some believe that in every case of rheumatic fever the heart is involved—subclinically in some and in others with obvious damage to the heart. A good many of the pathologists, when death occurs from some accidental means and in

the course of rheumatic fever, will find microscopic evidence of involvement of the heart, but how are we as clinicians going to make the diagnosis? Of course, there is the matter of our usual physical examination—is the heart enlarged? I don't think the enlargement of the heart is definite evidence that the child has rheumatic fever. We can determine more definitely about cardiac enlargements by the use of the fluoroscope or the x-ray than we can by the physical examination but I don't think the fact that we find a little evidence of cardiac enlargement or a little increase in the left ventricle is definite evidence that we have heart disease. We know that we have electrocardiographic changes in rheumatic fever, particularly if we take repeated electrocardiograms. I don't think that from single electrocardiograms we have a right to diagnose rheumatic fever. And I think if you have serial electrocardiograms that are compatible with rheumatic fever you should still hesitate before saying that the changes are necessarily on a rheumatic basis. I think the most important part of a physical examination is the use of the stethoscope and I want to talk a little bit about what one hears when he encounters early rheumatic heart disease. I am sure all of you have had the experience of having a child who has a typical attack of rheumatic fever come down with acute joint pain. That child enters the hospital only 3 or 4 days later and you hear at the apex a soft blowing systolic murmur not previously present. This is highly significant. Now can we say that that child has vegetations on the mitral valve which produce that systolic murmur which we hear with transmission to the left? Or is that due to an accompanying myocarditis perhaps with a slight enlargement of the heart which gives one a relative mitral insufficiency? I think perhaps that cannot be answered because we don't see these early cases at the autopsy table and I don't think it is important because I do think it indicates the presence of organic heart disease on a rheumatic basis.

I want to emphasize that that murmur is near the apex or at the apex and not over the base of the heart. If the child progresses as many of these children do to a more severe involvement of the heart before long one is likely to hear a murmur in early diastole, the so-called mid-diastolic rumble. I think that is evidence of cardiac involvement in addition to the presence of systolic murmur. I don't think this murmur is talked about as much in adult cardiology as it is in children but certainly it is often a distinct rumble, not a blowing sound, but sort of an echo of the second sound and first of all perhaps no more than a third heart sound. As time goes on you begin to get a definite rumble which is more than a mere sound coming at about the time of the third heart sound. Still later if the involvement of the mitral valve progresses, one gets an additional murmur, the so-called presystolic murmur which you are familiar with, usually heard at a localized area over the apex. Unless you get the stethoscope in exactly the right spot you may miss it. I should emphasize that in all these cases you should be listening with the child lying down and not sitting up. In hunting for the presystolic murmur one should not be content to listen to the child lying on his back; he should also be turned on the left side in a comfortable position and rolled back and forth a few times to get the presystolic murmur.

To my mind, those are the murmurs which one hears at the apex of the heart in rheumatic heart disease. A good many children develop the systolic murmur and nothing more and in some of these the systolic murmur may disappear. I don't think the fact that it disappears means that child did not have any heart disease but that he had a mild form of heart disease which healed sufficiently so that you no longer hear the murmur. Now when it goes on to the development of a presystolic murmur, then the evidences of involvement are usually permanent.

As I say, those murmurs are at the apex. There is one other murmur which is important. We know that the mitral valve is involved in practically 100% of patients that come to autopsy having had rheumatic heart disease. The second most frequent valvular involvement is that of the aortic valve. The early aortic valve involvement, of course, is that of aortic insufficiency and as a result you get a soft blowing diastolic murmur beginning with the second sound. I want to emphasize that—beginning with the second sound and not at an appreciable interval after the second sound. It is heard best, not over the aortic area, but usually over to the left of the sternum at the third left interspace. Sometimes I become a little dogmatic with my students and say that as far as rheumatic heart disease in children is concerned those are the only 4 murmurs you need to worry about. Those are about the only murmurs you hear in rheumatic heart disease of children and while that is not quite 100% true, I think it is a good thing to keep in mind as being important.

Tricuspid valve disease is so similar to mitral valve disease in the physical findings that you probably are not going to be able to differentiate. The mitral valve is usually more involved than the tricuspid valve and overshadows the findings you get in the tricuspid area. I will admit that late in

childhood you may get an aortic stenosis following or accompanying an aortic insufficiency; it is not very common and even then the insufficiency, in my experience, is usually a more important physical sign than the aortic stenosis. So far as pulmonary valve disease is concerned in rheumatic heart disease it is practically nonexistent from the clinical standpoint. You get a few cases at autopsy that will show involvement of the pulmonary valve, usually not very extensive and not clinically important.

Question: Can you rule out congenital heart disease?

Chairman Gibson: I would like to say something about the differential diagnosis of congenital and rheumatic heart disease. I have seen children put to bed for 6 months or even a year with congenital heart disease on the basis of the murmur with no signs of any particular incapacity. Let us just think what produces a murmur in congenital heart disease: ventricular septal defects, auricular septal defects, patent ductus arteriosis, pulmonic stenosis, in some instances aortic stenosis. The thing that I would like to emphasize is that in congenital heart disease almost all the murmurs that you hear are definitely above the apex. Now the most important murmur in rheumatic heart disease is the mitral and how many congenital cardiac conditions are there in which your murmur is actually maximum at the apex particularly with the same transmissions that the murmur has which you encounter in mitral insufficiency?

I know that the murmur of a ventricular septal defect can be pretty close to the apex. I think there is one extremely important differential diagnostic point in doubtful cases. If I can feel a systolic thrill I consider it is practically diagnostic of a congenital cardiac condition rather than a rheumatic condition because a systolic thrill in a rheumatic mitral insufficiency is pretty rare.

Question: Is the quality of a murmur of extreme importance in determining the difference between a congenital lesion and a rheumatic lesion?

Chairman Gibson: By all means; I think that often the murmur of the congenital lesion has a harsh rasping quality which you do not often associate with the rheumatic lesion.

Dr. Moore: I get the impression that we have much less joint involvement than you see in the North. I spent some 3 or 4 years in a rheumatic heart clinic and covered the central part of South Carolina and we certainly saw a lot more carditis without any involvement of the joints than we read about. I was just talking about a patient I saw with a severe carditis who had been admitted to the hospital 4 weeks ago with a severe abdominal pain; he was thought to be a surgical case and discharged as a typical gastroenteritis. Three weeks later the patient came in with a severe fulminating carditis and died some 2 weeks later. We have seen several similar cases in the past 5 or 6 years.

Chairman Gibson: The prevention of rheumatic fever has come into increasing prominence because of certain discoveries on preventing recurrences.

Dr. Baldwin: It is generally conceded that prolonged use of daily oral penicillin or sulfonamide in rheumatic subjects has decreased the incidence of recurrences of active rheumatic fever. As the chance of recurrence appears to be greatest within the 5 years following an active episode, it would appear that prophylaxis should be maintained during this period of time. It has seemed wiser to continue prophylaxis throughout the year.

Chairman Gibson: I rather am in favor of sulfa as opposed to penicillin because we certainly haven't had nearly as many cases on penicillin as we have had on sulfa and sulfa has produced remarkably good results. I heard Dr. Rammelkamp out in San Francisco a year ago say that in his opinion, in the present state of our knowledge, sulfa was preferable to penicillin as a means of preventing recurrence of rheumatic fever.

In our hospital the patients with rheumatic fever are kept until we think the active signs are gone and there is a normal sedimentation rate, they are eating well and gaining well and have normal blood counts and no further anemia. Then we put them on gantrisin®, which is less likely to have side effects than any of the other sulfonamides, and send them home and keep them on it the year around. I don't believe there is any good logic in omitting it from the first of July until the first of October. If you are going to do the job you ought to do it right and plan a 5 year program of giving it every day, day in and day out during the entire year.

We have been playing around with sulfa prophylaxis for a long time and we have some pretty good figures. I think we shall have to try penicillin for some time before we can draw any adequate conclusions:

New Speaker: We have always felt that dropping it for 2 months in the summer is giving a break.

New Speaker: We in Toronto have as much rheumatic fever during the summer as in the spring

and we get many streptococcic infections throughout the summer, as any of the practicing pediatricians will tell you. So we do keep it up all summer and are using sulfa in part because of economic reasons. There is another angle to the danger of penicillin which I don't think has been emphasized: that is the danger in penicillin therapy in allowing other nonsusceptible organisms to play havoc, particularly the gram-negative organisms. It is much more true in infants; it does seem to hold in children. It has been figured out at $100.00 a year for daily doses of penicillin at 300,000 units.

I would like to have Dr. Gibson talk about this new technic of treating streptococcic infections as they come along, to prevent recurrence of rheumatic fever.

Chairman Gibson: That will be discussed under treatment. I think that before we leave the subject of prevention of rheumatic fever, we should mention the work of Dr. Robert Jackson in Iowa City who has carried out rather extensive studies among rural children in Iowa. He emphasized particularly the general care and diet of these patients who have had an attack of rheumatic fever. A nurse is sent into the home to investigate the entire family environment: whether the child sleeps alone, with other children, in the same bed or in the same room. Clothing is taken into account and particularly whether the child has a diet adequate in protein. Jackson feels his results are almost as good in preventing recurrences as the use of some sulfa drugs. It is easy to give a pill; we are apt to forget that these children need general physical and medical care. That is apt to be neglected in our management of the child with rheumatic fever.

There is one other thing we should mention before we leave the matter of prophylaxis and that is the work of Dr. Rammelkamp and his group in giving penicillin in the early stage of streptococcic sore throat. I was delighted to hear Dr. Rammelkamp say that in his group (soldiers with whom he is working in Wyoming) he can look into the throat and decide whether he is dealing with the hemolytic streptococcus. From his wide experience he found that his clinical examination checked with the study of cultures in about 90% of the cases. He found also that in an old rheumatic patient subject to recurrence, if given penicillin during the first 48 hours (preferably hypodermically for at least the first 2 or 3 doses and then orally) and kept on it for a few days, the incidence of recurrence was much lower and was statistically significant.

We will now take up the subject of treatment of rheumatic fever, particularly rheumatic heart disease. Now in the treatment of rheumatic fever we know everybody is agog over the use of ACTH and cortisone in these cases. I think those things should be discussed here because most of us are familiar with what has been done in the past for rheumatic fever.

Dr. Lambert: My experience is obviously limited in that field but it corresponds and I think there is remarkable agreement that there is a dramatic effect on the manifestations. There is general agreement that it does not affect the natural course. If the drug is stopped before the disease has run its course, the manifestations will return. Chronic disease cannot be affected. Previous damage cannot be affected; there is considerable agreement to that effect. That a number of children have probably been saved from dying of rheumatic fever is the feeling but obviously we have no proof. In the early stage it is strongly suggested that these drugs may affect the heart. The proof may not come for 10 or 15 years.

Chairman Gibson: Someone has said that ACTH has enabled the patient to walk to the autopsy table and that remark may be more or less true in a good many conditions. The suppression of symptoms in many instances is certainly remarkable and we must be on the alert for complications.

Dr. Baldwin: I have the feeling that with hormone therapy the earlier you treat, be it hormone or not, the possibility of success is probably better because you may break through the unknown X factor we don't know about in the early stage.

New Speaker: Let me inject a warning here about the use of ACTH; it can be a serious thing. We have had 2 serious accidents with ACTH.

Chairman Gibson: You have had no fatalities?

First Speaker: No.

Chairman Gibson: There is one other thing we might mention when we talk about complications. We all recognize that there are a number of things we have to watch out for when administering ACTH and cortisone. We had a child in the hospital who was treated with ACTH, which I am inclined to think saved her life. I have never seen a child so near death and still recover. We gave her about 120 mg. ACTH over a 24 hour period and she finally pulled through. She had serious heart damage and had been a rheumatic for a considerable time. She was kept on cortisone for a period of 4 weeks. At the end of that time she developed a psychosis; she turned against her parents

and everybody in the hospital and hated them all. This acute condition was really striking.

Question: How old was the child?

Chairman Gibson: She was about 9 years old. The condition lasted for about 10 days and then she snapped out of it and her previous good behaviour returned.

Would you recommend at the present time ACTH or cortisone in the routine treatment of early rheumatic fever?

New Speaker: As long as we know that aspirin will not prevent permanent damage to the heart and we don't know whether ACTH will or won't, we must use ACTH until we get an answer one way or another.

New Speaker: We have had a pericarditis develop on large doses of 200 mg. ACTH given every 6 hours—this in an extremely ill child. She developed a full blown pericarditis which lasted for a period of 2 weeks. Ultimately she recovered; perhaps the ACTH helped.

Chairman Gibson: My experience has been that in any particular episode of rheumatic fever, if carditis is going to develop, it develops early. I have rarely seen a child come into the hospital, have joint pains which then subside and a normal temperature for a period of a few weeks and later on flare up with a severe carditis. If a child should have a flare-up perhaps ACTH could be used at the time it occurs rather than at the beginning.

I know we have that slow creeping type that involves the heart, perhaps without the obvious manifestations we usually have, but I think those cases are in the minority.

Question: Inasmuch as bed rest is an important part of the treatment, what is the time limit on the bed rest? And how long for the patient who has had ACTH or cortisone?

Chairman Gibson: That is the eternal question and always hard to answer. I would like to be a little conservative. I don't believe in the long bed rest periods that used to be carried out but I do think that one should keep the child in bed until the temperature is normal and has been normal for some time without salicylates. I wait until the child has an improved appetite, is gaining weight, has a good color and a normal sedimentation rate and a heart that is relatively quiet and then, as I have always said, after I look all of these things over I turn to the head nurse and ask her whether the child is ready to go home. She sees the child several hours a day, she knows the little complaints and she knows whether he is in reality convalescent. Now that period of time varies; I seldom let a rheumatic patient go home under 3 months on general principles because I think we don't know just how long the active infection lasts. There may be something lingering there after our tests are normal. If there is cardiac involvement, of course, the time is even longer. I don't know whether we should let an ACTH-treated patient get up soon after the ACTH or not. I think we should keep him down until we find out more about what is actually going to happen to the child.

I would like to mention the work being done at Herrick House which is a convalescent rheumatic fever home in the outlying region near Chicago. The children are quite carefully controlled, have good medical supervision, good food and good nursing care. It has been our idea for some years that after the acute stage is passed and the children go into the convalescent stage, that the convalescence has been too much prolonged. Now we have carried out on several hundred children this idea of early ambulation. Once they are active we have allowed these children to progress rapidly from relative inactivity to practically full activity where they can go out and play ball and swim, etc. Up to the present time we have not had any reason to think that is not a good thing. I think that 2 mistakes are often made in the general management of rheumatic fever: (1) the child is not kept quiet enough during the active stage; (2) the child is not allowed to do enough after the active stage is passed. I put the question to a cardiac physioiogist not so long ago: I said, suppose we have a child who has distinct cardiac damage from rheumatic fever. Assuming also that this child is completely free from active rheumatic infection, do you know any physiologic reason why that child should not be allowed to exercise up to the point of fatigue? He said he knew of none. That is an important practical point worth keeping in mind.

Chairman Gibson: The subject of rheumatic fever, of course, is of great interest because of its frequency and partly, also, because it has been much better advertised in recent years than previously. One can't pick up a lay journal without reading about rheumatic fever and the ravages of heart disease. Physicians have consequently become very conscious of the possibility of rheumatic fever in their patients and I have a distinct feeling that as a result of all this publicity rheumatic fever is often over-diagnosed.

Of the patients referred to me for possible rheumatic fever, in a good many I am not able to find it. On that account I think we should discuss, at least to some extent, the points in the diagnosis of rheumatic fever. We will take up etiology and recognition of rheumatic fever and then the prevention of rheumatic recurrences.

Dr. Lambert: The prophylactic evidence is the most practical and most interesting at the present from the pediatrician's point of view. But it seems to be well demonstrated and well established that daily administration of sulfadiazine and probably daily administration of penicillin is effective in significantly reducing the incidence of both tonsillitis and of rheumatic fever. More recently it was found that in such incidences of anticipated rheumatic fever in children with previous attacks and in control series, the initial attacks of rheumatic fever can be prevented by treating a streptococcic infection in the first 24 to 48 hours. It is of interest here that this same intensive treatment in early infection will prevent the rise of antistreptolysin over antibody titer. Experimental evidence consists of the demonstration of lesions closely resembling rheumatic carditis in small animals that were injected with various types of group A streptococci.

Murphy and Swift did that work in 1949 and I am not aware that it has been duplicated. They are extremely careful workers and it certainly is suggestive evidence.

The mechanism of rheumatic fever is no where as clear as the evidence for the streptococci theory. The most fashionable concept and the one for which there seems to be the most evidence is the allergic one. The clinical evidence for that has long been obvious. People have thought about that since 1900 because of the closc resemblance to serum sickness. Serum sickness not infrequently offers a tough differential with rheumatic fever.

(Chairman Gibson discusses recognition of rheumatic fever; see p. 492-493.

Dr. Frederick Rittinger, Cleveland: I would like to ask whether the pain is always necessary in these cases. Is it possible to have stiffness in the joints? What about these cases where the mother says that the child gets up in the morning and is stiff in the legs?

Chairman Gibson: I think one simply has to reserve judgment in cases of that sort; I don't think you can make a definite diagnosis of rheumatic fever. One wants to know, too, in that connection whether the child has fever, whether the child is actually ill. I couldn't say that a positive diagnosis could be made on that evidence.

Dr. Leon DeVel, Grand Rapids, Mich.: Would you say that there is an importance in the age status in that the younger the child the more the joints are affected? When you come to the adolescent, they are apt to be in the foreground.

Chairman Gibson: I think that is very true. I have seen undoubted rheumatic carditis in rheumatic children—several patients under the age of 3 years, not very many, because we know that rheumatic fever which we can recognize clinically is rare under that age. I think the joint pains are apt to be pretty much in abeyance until the age of 5 or 6 years. Of course, with the child of 3 years, while he may be acutely uncomfortable, he can't tell you so well exactly where his pain is, but he may show you by his unwillingness to use some extremity. Unless the joint pains go on to redness and swelling, one may not be so conscious of the presence of joint pains but it is true that you will sometimes see severe rheumatic carditis without obvious joint involvement, particularly in the younger child. We know that the average age of onset of rheumatic fever is around the 6th or 7th year.

I would like to bring out one thing here—from the attendance list we have a number of doctors here from the South. I have talked to a number of physicians from the South and from what I am able to gather, rheumatic fever is presenting a somewhat different clinical picture when seen there than it does in New York, Chicago, Boston and farther north. Are the joint pains less significant, less prominent than they are in the northern climate?

Dr. Martin J. Harris, Louisville, Ky.: Joint pains do not hold the same prominence in the early manifestations of rheumatic fever.

Dr. J. A. Caprile, Buenos Aires: We encounter the joint pains frequently.

Dr. George S. Palmer, Tallahassee, Fla.: Our temperatures vary from freezing to 100° and joint symptoms are not common at all. Usually if they have aching joints it is an injury—actual infection but not a rheumatic joint.

Chairman Gibson: Many of these children who complain of pain probably have flat feet or other orthopedic disturbances.

Dr. R. A. Craig, Kokomo, Ind.: I believe that these pains persist in one particular joint for a much longer time than they do in other joints—that is, in a true rheumatic joint.

Chairman Gibson: I think one should be rather skeptical about it if it persists for a long time, particularly if salicylates are used. Sometimes it takes months to make a differential diagnosis between rheumatic fever and rheumatoid arthritis.

In my experience the genuine rheumatic pains subside spontaneously after a short period ordinarily and they subside overnight with the use of aspirin or salicylate.

Dr. Weindenthal, Cleveland: In 30 years of practice my incidence of unquestioned rheumatic fever has been very low, I would say not more than 2 in 30 years.

Chairman Gibson: I think we have to remember this: the Heart Association uses as its slogan, "One out of three die of heart disease." Now if you break down the types of heart disease about 1 out of 4 cases of heart disease is on the basis of rheumatic fever. If we can accept those figures, one out of 12 individuals dies from rheumatic heart disease. They must come from somewhere! We must remember that 75 or 80% of all our children in the country are taken care of by the general practitioner, not by the pediatrician. The pediatrician, particularly if he practices on the "Boulevard," doesn't see relatively poor children in the stratum where rheumatic fever is the most frequent. I think some pediatricians in some areas will see much more rheumatic fever than other pediatricians in the same city.

Dr. Harris: I am physician to a convalescent home in Louisville where most of the rheumatic patients gravitate for their convalescent care. I think that might be a good index in a city of about half a million and I would say that there are between 15 and 20 cases in the home.

Chairman Gibson: We will now move on to our discussion of chorea. In the past this has been considered very definitely a rheumatic manifestation. More recently there has been a little doubt about the rheumatic nature of chorea. I am sure that you are all so familiar with the picture that we do not have to discuss the diagnosis of chorea. I look upon Sydenham's chorea as a disease with a definite beginning though we may not be able to establish the exact date. The child has purposeless movements—they increase up to a point, then they go along for a few weeks, sometimes a few months, before these movements begin to subside. Finally these movements do subside and the child is again apparently in perfect health so far as his nervous system is concerned.

I should like to emphasize that along with these purposeless movements there is an equally important symptom which we too often neglect as a part of our diagnosis and that is the emotional instability which is practically always present in the true state of chorea. I think that the differential diagnosis of chorea can be a little difficult once in a while but not often. If you see a child with multiple tics, multiple habit spasms, it sometimes is a little difficult to differentiate from true chorea unless you watch the child for some time. These movements are stereotyped and the same movements are repeated rather than the varied movements which are so characteristic of chorea. Recognizing this as the true picture of chorea it has long been accepted as one of the major manifestations of rheumatic fever. It is true that in the uncomplicated case of chorea one has a normal temperature, normal sedimentation rate, no increase in the white count. In other words, we cannot establish by laboratory means the existence of actual infection. On that basis can we say that chorea is perhaps not a rheumatic manifestation, or can we say that because of the location of the rheumatic process in the chorea child we may not get the same reaction? Perhaps brain tissue does not react in the same way that joint tissue does or not to the same extent so that maybe we are dealing with a so-called subclinical rheumatic fever in the child that actually has a chorea.

Dr. Alfred G. Langmann, New York City: I am not aware how you can differentiate those. I know that Dr. Jones has distinguished pure chorea; he said that in pure chorea only about 3% develop cardiac complications. But Dr. Samuel A. Levine in Boston says that in some of these patients with so-called pure choreas, they find definite mitral stenosis when they reach the third decade of life without any intervening acute rheumatic manifestations. So perhaps we have to change our view about so-called "pure" chorea patients.

Chairman Gibson: I have had the experience of seeing mitral stenosis often in a child following chorea.

My feeling is that the best way in doubtful cases of chorea, if you want to make an effort to bring out the more active movements, is to put the child under stress. I ask a child a number of questions, how many brothers and sisters he has, where he lives, what is his address, and then I particularly ask the child to count. The child will start in to count, perhaps stammer a little, stop and take a deep breath and then start in again rather rapidly. Then if the child is old enough I will

ask him to count backwards. Something that makes that child concentrate almost always will bring out the movements you do not see when the child is mentally at ease.

Dr. Harold X. Gerber, Chicago: It is my impression that in the last 8 or 10 years there is less incidence of chorea.

Chairman Gibson: Perhaps the diminution in chorea parallels the diminution in rheumatic fever. There is still a good deal of dispute as to whether rheumatic fever is less prevalent now than it was. From my experience, I think that it is. Back in the 1930's we had 35 beds for rheumatic fever; one year we had our entire 35 beds filled in July with rheumatic fever cases and since the other wards weren't so busy we had 15 other cases on another ward. Fifty cases of rheumatic fever in the house at one time. Our average in the house right now is about 8 or 9 cases. Certainly the mortality has diminished since the 1920's and probably rheumatic fever has.

We will now go on to skin manifestations.* One important one is erythema annulare. I think this is a descriptive term. Most of you have seen it at one time or another. It is truly an erythema—no swelling, no elevation of the skin. This erythema consists of a pink narrow line appearing most often on the trunk and on the upper arms and legs. I have never seen it on the face.

It does not occur frequently in my experience. If it does occur in a rheumatic individual, it is extremely likely to recur over a period of days or weeks.

(See p. 496 for discussion of rheumatic nodules.)

Dr. Thomas M. Lamb, Brooklyn: It is my opinion that rheumatic nodules are much more frequent than is generally thought. It has been really a challenge to us when a child is admitted for rheumatic fever to find the nodules. Where we only found them in 15 to 20% of the cases, Dr. Sutton, when she came on, found them in 50% of the cases and she demonstrated them to us.

Chairman Gibson: If the arms are straight and relaxed you don't see them but if you flex the arms or the legs sharply you are much more likely to see them and even though you emphasize the fact that they are common on the knees or elbows, they may be many other places—the scalp, wrists, ankles, spines of vertebrae, flexor tendons of wrists, knuckles.

Dr. Craig: Do you use sulfa on the chorea patients over a long period?

Chairman Gibson: That is a hard question. I would not think it necessary if there were no other signs of rheumatic fever.

Dr. J. R. Schroder, Janesville, Wis.: Has anyone had any experience or any work with sulfa that tends to show that prolonged use of sulfa may produce periarteritis?

Dr. Lambert: I know indirectly the Yale experience where they made autopsy studies on patients who had sulfa reactions. They found a fairly high percentage of periarteritis nodosa lesions and these weren't just microscopic findings. Also Dr. Rich was able to produce a periarteritis nodosum-like picture in animals by giving sulfa but it just doesn't seem that these children are bothered by it. We may be all wrong but in 10 or 15 years nothing more striking than that has come up.

We keep our children on sulfa when we are sure they have had rheumatic fever, particularly when there is evidence of cardiac damage. We try to keep them on it for 5 years and the parents are told that if the child gets a sore throat with fever that the child should be brought immediately to the clinic. We start him on penicillin and try to keep him on penicillin for 10 days. We are going to start using it orally because it is much more convenient and it is not very expensive. That type of treatment in practice is estimated at about $7.50 each time the child gets a real sore throat.

But if you take rheumatic fever just as seriously as you take tuberculosis, and you should, it represents a practical program and an important one. More can be done with this program at the present time than with ACTH and cortisone.

Chairman Gibson: I would like to emphasize that in the treatment of active rheumatic fever when we get a spectacular drug or means of therapy we are too likely to forget the ordinary things that should be done in the child's general care. The child with active rheumatic fever should be put to bed and given all the attention that the physician would have given him before the introduction of ACTH or cortisone.

Everyone should appreciate that in the use of ACTH and cortisone, whatever the condition may be, you are very likely to mask symptoms and make the patient much more comfortable. Any patient who is on ACTH or cortisone has to be most carefully watched.

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* See p. 495 for discussion.

It is generally agreed that ACTH or cortisone will make the patient comfortable. They will usually reduce the temperature to normal and also the sedimentation rate will come down in a relatively short time. In some instances, new murmurs will disappear and the patient will appear practically well. That doesn't necessarily prove that we have cured the patient and those carrying out this study are still extremely cautious about saying that we are really protecting the patient's heart by the use of ACTH or cortisone. Some of you probably saw in the last issue of the *American Journal of Diseases of Children* the article coming from the Mayo Clinic by Dr. Barnes and his associates. They reported that perhaps the use of these hormones would tend to cause a suppression of the condition in the exudative stage and that perhaps the proliferative stage is lessened with, consequently, less damage to the heart. Certainly it is the development of the Aschoff's bodies and the changes that take place in the heart muscle that cause the serious damage to the heart.

Now if ACTH and cortisone will do that, and Barnes and his co-workers and others have some evidence to the effect that it will, there is something hopeful in the use of ACTH and cortisone in rheumatic fever. I don't think that anyone else in the country has achieved the same brilliant results that May Wilson reports in her group of cases.

I think, and I'm sure Dr. Wilson would agree, that those patients have to be followed for a considerable time before we can really say whether they are cured. Yesterday Dr. Baldwin, who is part of the cooperative study on ACTH and cortisone, described 2 or 3 of her cases. She has one group on ACTH and cortisone and a control group on salicylates. She remarked that at least 2 patients had responded to salicylates just as beautifully as they had responded to the hormones. So it is going to be a considerable time yet before we know.

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SPECIAL SECTIONS

TRENDS

BY JOHN P. HUBBARD, M.D., *Contributing Editor*

Statements appearing in this column do not necessarily reflect the opinion of the editor nor are they to be interpreted as the official opinion of the Academy.

THE value of the state reports of the Study of Child Health Services continues to be reflected in activities within the states under the leadership of the Academy. A brochure under the heading "Child Health Is Everybody's Business"* has just appeared and describes progress and goals in New York State. This booklet is based upon the state survey and more recent recommendations of the State Citizen's Committee for Children and Youth. It is illustrated in lively fashion and will undoubtedly play an important role in the improvement of child health, not only in New York State but elsewhere as well. Its value cannot be fully appreciated without the visual stimulus of its illustrations by Barbara Pfeiffer of the Metropolitan Life Insurance Company staff. Nevertheless it has been so thoughtfully prepared that, with the approval of the state group, we have summarized it in the following pages.

"Child Health Is Everybody's Business" is being given a very broad distribution throughout New York State. Individual copies are being sent to each member of the American Academy of Pediatrics within the State. The Medical Society of the State of New York has sent several copies to each County Medical Society, with the suggestion that additional copies be used by the members of committees on child health and on school health. In New York City, voluntary health agencies and related organizations are being reached through the City Health and Welfare Council. In upstate New York, the newly formed State Health Council has distributed copies to its membership; local tuberculosis and health associations have been reached through the State Charities Aid Association. Direct distribution has also been made to all local Parent-Teacher Associations. Local health departments and district health officers of the State Health Department supplement this distribution locally. Individual copies are available to physicians and other persons out-

* Joint publication: New York State Study Committee, American Academy of Pediatrics; Child Health Section, New York State Citizens' Committee of 100 for Children & Youth; Medical Society, State of New York, & Bureau of Maternal & Child Health, New York State Department of Health. Published by the Office of Public Health Education, New York State Department of Health.

side of New York State from the Bureau of Maternal and Child Health of the New York State Department of Health.

This booklet has been prepared for the use of those to whom the health of children is important. It is intended as an aid to physicians, educators, community health and welfare leaders, and other citizens for reviewing the health services for children in the community and for taking those steps that may be needed to correct any existing deficiencies in these services.

This report highlights some of the important findings of the New York State Child Health Study, made in 1946 and 1947 by the American Academy of Pediatrics with the cooperation and help of the Medical Society of the State of New York, the Dental Society of the State of New York, the New York State Department of Health and many other agencies and individuals concerned with child health. It includes a number of the recommendations made by the New York State Citizens' Committee of 100 for Children and Youth in its activities relating to the Midcentury White House Conference of 1950. These recommendations suggest ways and means to strengthen or improve present health services for children. The questions and suggested projects at the end of the booklet are illustrative, and by no means inclusive, of what interested citizens, professional and lay, should consider in order to reveal the extent to which each community is meeting the health needs of its children and youth.

What do we seek in the way of better health for the children of New York State? The professors of pediatrics in the nine medical schools in New York State prepared a guide at a meeting called by the Child Health Section of the State Citizens' Committee in 1950. The pediatricians offered this goal:

"In the provision of health and related services the definition of health formulated by the World Health Organization should be kept in mind, i.e., 'a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.' All children in the State should have the benefit of adequate total health supervision from birth through adolescence to aid them in attaining such a state of health. In New York State, with its existing and potential resources, it should be possible during the next decade to achieve this goal of providing adequate total health supervision for all children in the State."

Every activity today is subject to the acid test of its potential contribution to the defense effort. Viewed in this light, the report can serve as timely evidence to the citizens of New York State of the scope and value of health services for children. The well-being of our children is of the utmost importance now and in the future. To promote and maintain our children's health is everybody's business.

The following essentials of health supervision are deemed necessary for the healthy growth of our children from birth through adolescence: Favorable emotional climate, medical care, adequate diet, communicable disease control, accident prevention and dental care. Most of these factors are dependent on the knowledge and understanding of parents. Parent education, therefore, is a basic and continuing requirement for adequate child health supervision.

New York State is rich in physicians. It has one-sixth of all the country's physicians, one-fifth of all the country's pediatricians. The ratio of 378 physicians to 100,000 population found in the most rural areas of New York is higher than that for the United States as a whole, which is 325 per 100,000. However, the advantage of this ratio is reduced by the following factors: (1) these physicians are concentrated in big cities, especially

in New York City; (2) children in up-state counties received 20% less private medical care for illness and 40% less health supervision, and (3) one-third of the general practitioners reported little or no hospital training in pediatrics, yet general practitioners render the bulk (70%) of private medical care for children.

New York state exceeds the national average in child health services but they are unevenly distributed: 80% of the Child Health Conferences are in New York City and its surrounding counties. Compared to other states, New York school children have more medical and nursing services. However, although almost all schools employ a physician to give medical examinations, as required by law, not all schools have nursing and dental hygienist services. Immediate professional supervision of doctors and nurses is very limited outside the large cities of the State. Mental health services are centered in major cities, and even where they exist they usually have long waiting lists.

New York, although it ranks fourth among the states, falls about midway in the amount of service provided children in dental clinics—to its 65 dentist hours per 1,000 children, Massachusetts gives 121 and Maryland and the District of Columbia, 119. Rural areas lack adequate preventive and treatment services for children. Of the dental service available in the state of New York, children in the New York City area receive the bulk of the service.

The 30,000 crippled children receiving care at present in New York are believed to represent most of the state's children with visible handicaps. However, while the state's record is good in comparison with other states, children outside the larger cities with handicapping conditions such as cerebral palsy, cleft palate and lip, hearing defects, and speech defects, aside from the correction of the physical defect, do not have the benefit of retraining and other important aids in rehabilitation. Even some of the large cities do not have complete speech or hearing services for children.

There are 2,320 public health nurses, exclusive of those in schools and industry, which means one nurse for every 1,276 children. But, while the number of public health nurses in New York is double the national average, this is still less than half the number needed for satisfactory public health nursing services.

Local health units are the most efficient way of providing most, if not all, of the special child health services to the community. However, they are slow in forming despite a recent increase in the amount of State aid for this purpose.

The staffing and services for care of children in hospitals exceeded the average for other states when judged by standards developed by the American Academy of Pediatrics for the nation-wide study. However, deficiencies, largely confined to the smaller hospitals, reduce the effectiveness of the hospital care for children.

Prematurity is a chief cause of death in infancy. Deaths from this cause, of all causes of death in early infancy, are probably most easily prevented. The following figures call attention to the great loss of life resulting to a large degree from inadequate facilities for the care of premature infants: Sixty per cent of the hospitals lacked a separate nursery for prematures; 10% of the hospitals with a separate nursery did not have a graduate nurse on duty at all times in the nursery. A way to meet this problem is to have special premature nurseries established in hospitals where 1,000 or more births occur yearly. The small hospitals could then send their prematures, in specially provided incubators, to the special nurseries.

Infants and preschool children in New York State are in a highly favorable position when compared with the national average and with other leading states. This superiority on the national level applies both to health supervision received through private physicians

as well as in public services such as well child conferences. Today physicians are focusing more of their attention on the prevention of accidents and disease. The pendulum is swinging toward continuing health supervision of the well child, including not only regulation of the infant's feeding and immunizations in the first year of life, but also health guidance to insure the best possible physical and emotional growth. Well child conferences in New York State exceeded the national average, but they are much more common to the urban and suburban areas. While 179 per 1,000 children under 5 in the Greater Metropolitan Area received care of this kind, only 42 per 1,000 were served in the rural areas. Since 1947 there has been a marked increase of about 50% in the amount of child health supervision given through child health conferences. Despite this, no reason for complacency exists. It is still necessary to tackle deficiencies in the areas where they are known to be present. A remedy for the situation might be found in: (1) greater use of health education to teach the public the value of periodic health supervision by their family physician, and (2) establishment of child health conferences to show the value of health supervision to those who otherwise would not receive this service.

Ideas of the factors needed to keep children healthy have changed in recent years. Emotional and social well-being are recognized as important and inseparable parts of the total health picture. More is known today about what is basic to the various elements essential to the maintenance of health. The task now is to apply this knowledge to the fullest. The following recommendations are aimed at that goal: closer working together of official and voluntary health services; recruitment and training of personnel working with children; education of those working with children to a better understanding of the emotional needs of children; extending facilities for recreation as one means of promoting normal emotional development; development of health services in areas lacking them; education of parents to the need and value of continued health supervision; raising the level of hospital care of newborn infants; a program to prevent prematurity and to give special care to premature infants, including the training of medical and nursing personnel, the development of special centers and the provision of transportation for such babies to these centers; making available community services to aid children with nutritional deficiencies; providing nutrition education to all pregnant women and additions to the diets of those who need them; maintaining and improving communicable disease control in children, and educating parents to make their homes and communities safe for children.

On a sample day nearly 20,000 children in New York State received dental care. Although this is more than double the figure for the nation, it still falls short by half of the actual dental care needed by children. How can the gap be closed between the dental care received and that which is needed? Children of this State receive approximately two visits per child per year, but dental experts say that four visits per child on the average are usually required to give complete dental care. Since the survey, much progress has been made in the prevention of dental decay: sodium fluoride has been added to drinking water in some localities and in many parts of the State it is being applied directly to the children's teeth.

Dental hygienists are playing a greater role in dental supervision and the application of decay-preventing substances to the teeth. Local application of sodium fluoride has been made available in many dental health programs operated by health departments or sponsored by local school authorities. The dental schools of the State have greatly expanded their programs for teaching children's dentistry.

Ways by which the gap between available and needed services might be spanned include

the following: broadening the program of parent education for greater use of existing services; making tested preventive measures more widely available; having organized community programs start with six-year-olds, or entering school children, giving previously enrolled children additional care as they need it; interesting more dentists in the care of children's teeth, and by extending the facilities for training in children's dentistry.

New York ranks high in terms of the ratio of handicapped children served to the total population and in terms of the total number of visits. But more emphasis on preventive measures is necessary to check crippling conditions. This can be done by applying the knowledge we already have regarding: congenital malformations, premature births, child safety and control of infections. Important factors which must be overcome include: lack of knowledge of families in rural areas concerning what can be done for these children, and an insufficient number of trained personnel to staff clinics.

Handicapped children have certain needs in common: (1) General Health Care, which is most effective if there is a coordination of all services for children with handicapping conditions on the community, regional, and State levels, (2) Favorable Emotional Attitude, created through professional and parent education, (3) Early Discovery of Handicap, (4) Evaluation of Handicap, (5) Adequate Treatment Facilities in the local community. The child should be separated from his family only if he is to be sent to an institution that can better tend to his needs, (6) The physically handicapped child should be permitted to attend regular classes in school, or, depending on his handicap, special classes in a regular school. Residential schools should be provided for those whose handicap is too severe to permit regular attendance, (7) There is a need for more rehabilitation centers in convenient locations which children can attend during the day. The centers should offer treatment to persons with all types of handicapping conditions, and to any child who can benefit from the services offered.

Individual disabilities of children call for specific measures.

Children with defective hearing need: more widely available diagnostic and rehabilitative centers; facilities for teaching lip reading and speech correction, and training in hearing; financial aid to help purchase and maintain hearing aids, when needed, if facilities exist for their proper selection and services are available for instruction in their use and for follow-up.

Children with rheumatic fever and heart disease need: adequate diagnostic and consultation services made available in the areas now without them; more facilities for the convalescent care of children with rheumatic fever since half the State lacks them; state aid for hospitalization and convalescent care extended throughout the entire State.

Children with dento-facial defects need: more dentists trained in the prevention and correction of dental irregularities; postgraduate programs for dentists to train them in this field; a broader distribution of these specialists; centers where children with cleft lip and palate can have the attention of pediatricians, surgeons, dentists, psychiatrists, medical social workers, speech therapists, and related personnel.

Children with impaired sight need: expansion of diagnostic services; more sightsaving classes, preferably on a county plan; grouping together of children of the same age in New York City sightsaving classes.

Children with epilepsy need: a community and school educational program that will increase understanding and acceptance of epileptics, increase their job opportunities, study the legal aspects of their affliction, and remove unwise social and legal restrictions; establishment of centers for diagnosis, treatment, training, and research; an integrated

medical, psychiatric, and social approach to their problem through the team work of medical and related specialists.

Children with other handicaps need: coordinated community planning for their care; more thorough rehabilitation techniques available in centers with complete evaluation of the child by a team of specialists in related fields; provision for custodial care of children with progressive incurable diseases and of severely handicapped children who cannot or should not be kept at home; further expansion and extension of present diagnostic and rehabilitation services for the cerebral palsy child.

Projects

Here are a few suggested projects:

(1) For parents: train your children to recognize and avoid accident hazards; seek health guidance for your child from your family physician.

(2) For physicians and dentists: educate parents to the need of continued health supervision. Participate in pediatric or pedodontic post-graduate education programs.

(3) For community leaders: organize a health council. Encourage physicians and dentists to settle in communities where they are deficient in number. Arrange for parent education courses on the health needs of children.

(4) For local medical societies: secure pediatric courses from state society. Sponsor clinics in local hospitals.

(5) For hospital administrators: arrange for exchange of services with a large medical center if you are located in an outlying county. Provide adequate pediatric facilities for newborn and other children. Strengthen pediatric training of nurses.

NEWS AND ANNOUNCEMENTS

A recent announcement has been made that Dr. Wilfrid Sheldon has been appointed a member of the Royal Household of Queen Elizabeth II. His title is Physician-Pediatrician. He is Physician for Diseases of Children, Kings College Hospital, London. His duties will consist of attending the health services of Prince Charles and Princess Anne. It is believed that this is the first instance of a pediatrician receiving an official position and title in the household of a royal family.

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Louisiana State Department of Health and Charity Hospital of Louisiana at New Orleans in cooperation with Louisiana State University School of Medicine and Tulane University School of Medicine will present a postgraduate course on the Premature Infant, Nov. 5 to 19, 1952.

This course is open to all physicians and should be of particular interest to pediatricians and public health officers. Registration—limited to 10.

Applications and request for further information may be addressed to: Charity Hospital of Louisiana—The Premature Infant Center, 1532 Tulane Avenue, New Orleans 12.

* * *

The Food and Drug Administration of the Federal Security Agency has announced its decision to permit the continued distribution of the antibiotic drug chloromycetin under revised labeling that will caution physicians explicitly against its indiscriminate use.

Reports of blood disorders attributed to chloromycetin led to a nation-wide survey by the FDA late in June of the case records in hospitals and clinics. The case histories turned up by this survey were referred to the National Research Council for its aid in evaluating the information. FDA's decision was based on the findings and recommendations of a special committee of the Council's Division of Medical Sciences.

The committee of outstanding authorities on hematology and infectious diseases was headed by Dr. John Holmes Dingle, Professor of Preventive Medicine at Western Reserve University, Cleveland. The committee considered the records of 410 cases of serious blood disorders, of which 177 were definitely known to have been associated with the use of chloromycetin.

In 61 cases chloromycetin was the only drug administered. In the remaining 116 cases other drugs had also been given. In both groups fatalities totaled 50%, attributable to aplastic anemia and related conditions in which the bone marrow has lost its ability to manufacture both red and white cells of the blood.

A group of 168 cases, including 97 cases of aplastic anemia, was eliminated from consideration by the committee because it was determined that chloromycetin had not been administered. A remaining group of 65 cases in which chloromycetin may or may not be involved continues under investigation.

The consensus of the Conference was as follows:

"1. Certain cases of serious blood dyscrasias (aplastic anemia, thrombocytopenic purpura, granulocytopenia and pancytopenia) have been associated with the administration of chloramphenicol.

"2. Although this complication has thus far been uncommon, it is sufficiently important to warrant a warning on the label of packages of the drug and in advertisements of the drug and the recommendation that chloramphenicol not be used indiscriminately or for minor infections.

"3. When prolonged or intermittent administration is required, adequate blood studies should be carried out.

"4. In view of the paucity of information at the present time the Conference hopes that further study of serious reactions to chloramphenicol and other drugs will be promoted. The records of the Veterans Administration and military forces could be of great value in providing some of the desired information.

BOOK REVIEWS

Emotional Disorders of Children, Gerald H. J. Pearson, M.D., New York, W. W. Norton Company, 1949, $5.00, 368 pp.

Written by a well known American psychoanalyst, this book brings together much psychoanalytically oriented material about children and their emotional difficulties. The author uses the case discussion method somewhat after the example of Dr. Richard Cabot.

Pediatricians will find this book valuable in acquiring better understanding of such disturbances as the neuroses, anxiety states, sex perversions and the psychoses. One section deals with methods of studying emotional disorders in children, another describes how children may be prepared for psychiatric examinations; this is followed by a discussion of what a psychiatric examination comprises.

The psychoanalytically-oriented pediatrician will have no difficulty in understanding concepts presented in this book, but those readers without such awareness will find the subject matter difficult to comprehend. For them a book published earlier by Pearson in association with Dr. O. S. English titled, "Emotional Problems of Living and Common Neuroses of Children and Parents," is recommended as a preliminary study.

Congenital Dislocation of Hip, Julius Hass, Springfield, Ill., Charles C Thomas, Publisher, 1951, $12.50, 405 pp.

This monograph presents a comprehensive discussion of all aspects of congenital hip dislocation, and constitutes valuable reading for both pediatrician and orthopedic surgeon. The author is well qualified to write such a book; he was associated with Lorenz for many years in Vienna, and was his successor at the Orthopedic University Clinic there.

Hass classifies congenital dislocation of the hip in 3 categories: (1) Typical, in which hip dysplasia is present at or before birth and is followed in some cases by dislocation after weight-bearing begins. He believes that heredity plays some part in etiology. Its predominance in females is considered due to differences in the male and female pelvis. (2) Atypical (teratologic) cases, which occur in conjunction with other defects of a congenital nature such as arthrogryposis, arthrocalarosis, and defects in the spine and lower extremities. (3) Isolated cases of specifically known etiology, such as obstetric dislocation, congenital syphilis, cerebral palsy, and x-ray injury.

Early diagnosis and treatment are emphasized, in-as-much as successful therapy is inversely proportional to the age of the child. During the first year of life, before weight-bearing begins, prophylaxis is almost always successful, consisting simply of an abduction splint or bar. Closed reduction of the hip is advised from 1 to 3 years of age, followed by a cast or splint to maintain abduction for several months or longer. From 3 to 5 years of age, closed reduction is attempted after preliminary traction. If this fails, open reduction is indicated. In children from 5 to 10 years of age, open reduction is the treatment of choice, sometimes accompanied or followed by a shelving operation. Other procedures such as subtrochanteric osteotomy are also needed in special cases. Over 10 year of age, only palliative surgical procedures are of any benefit.

Chapters on history, pathology, etiology, diagnosis, treatment and prognosis include a comprehensive review of the literature and are well illustrated. There is some repetition, but probably no more than necessary.

Your Baby and Mine, Myrtle Meyer Eldred, New York, The John Day Company, 1951, $3.75, 305 pp.

Written by a newspaper columnist specializing in child care, this book for parents provides an easy-to-read and practical guide on such varied topics as physical care, emergency first aid, dietary advice and solution of emotional problems.

The child is discussed from the prenatal period to adolescence. The common developmental characteristics for various ages are described, and problems relating to development are discussed in a straightforward and practical fashion. By and large the advice given is sympathetic, thoughtful, and considerate of the needs of child and parent alike. While there are occasional misinterpretations of scientific data, and some advice which may be questioned, for the most part this book presents accurate and helpful information. The author has kept abreast of modern developments as demonstrated by discussions of natural childbirth and rooming-in care of the newborn.